CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208912Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 208912
Review # 1
Jan 5, 2018

Drug Name/Dosage Form	***Dexamethasone Suspension Intraocular Injection***
Strength	*9%*
Route of Administration	*intraocular injection*
Rx/OTC Dispensed	*Rx*
Applicant	*Icon Bioscience, Inc.*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*4/12/2017*
Amendment	*6/19/2017*
Amendment	*7/7/2017*
Amendment	*8/3/2017*
Amendment	*10/2/2017*
Amendment	*10/16/2017*
Amendment	*10/17/2017*
Amendment	*11/14/2017*
Amendment	*11/16/2017*
Amendment	*11/21/2017*
Amendment	*11/30/2017*
Amendment	*12/5/2017*
Amendment	*12/7/2017*
Amendment	*12/11/2017*
Amendment	*12/15/2017*
Amendment	*12/21/2017*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Rohit Tiwari	Benjamin Stevens
Drug Product	Xinghua Wu	Chunchun Zhang
Microbiology	Hemlata Tamta	Nandini Bhattacharya
Biopharmaceutics	Parnali Chatterjee	Elsbeth Chikhale

QUALITY ASSESSMENT

Process	Nancy Waites	Daniel Obrzut
Facility	Jonathan Swoboda	Derek Smith
Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Xinghua Wu	Chunchun Zhang

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)	Adequate	8/22/2017	LoA: 2/20/2009 Reviewed by Rohit Tiwari
	Type V			NA		LoA: 12/1/2016
	Type III			NA		LoA: 8/23/2016
	Type V			NA		LoA: 1/19/2016

[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	105562	This product during IND development

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Complete	Acceptable *(refer to DS and DP reviews)*		Aaron Ruhland
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 208912, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product, Dexamethasone Suspension intraocular injection, 9%. All information request and review issues have been addressed and there are no pending approvability issues.

The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approval" recommendation was entered in Panorama by the the Office of Process and Facilities (OPF) on 11-29-2017.

NDA 208912 is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

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

DEXYCU (Dexamethasone Suspension Intraocular Injection), 9% is a corticosteroid indicated for the treatment of postoperative inflammation. The proposed product is a sterile suspension and packaged in a single dose 2-mL glass vial with 0.5 mL fill volume, to be administered intraocularly in the posterior chamber at the end of surgery. DEXYCU is provided as a kit which includes four individual sterile pouches to administer a single dose of 0.005 mL of 9% dexamethasone (equivalent to 517 micrograms of dexamethasone).

Proposed Indication(s) including Intended Patient Population	For the treatment of postoperative inflammation
Duration of Treatment	Single dose, 517 µg dexamethasone per dose
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 is dexamethasone, a white to off-white odorless [(b) (4)] powder. It is manufactured by [(b) (4)] The drug substance is referenced to DMF [(b) (4)] which was found adequate by Dr. Rohit Tiwari on 8/22/2017.

ii. Drug Product Quality Summary

Dexamethasone suspension intraocular injection solution is a non-aqueous, preservative-free, sterile solution for intraocular injection to be administered using a sterile single-use 510k approved syringe. The drug product is provided in a single-dose, 2 mL Type I glass vial with a 0.5 mL fill. Each single dose delivers 0.005 mL of 9% dexamethasone (equivalent to 517 micrograms of dexamethasone). Each vial is packaged in a carton along with an administration syringe kit assembly which includes four individual sterile pouches: a syringe guide and ring, a syringe, a syringe needle, and a syringe cannula, these components are either 510K clearance or 510K exemption for Class 1 device.

Acetyltriethyl citrate is the only excipient used in the formulation. It is a novel excipient and is qualified [(b) (4)] from P/T perspective (email communication with Dr. Aaron Ruhland on 12/7/2017). No overage is used in the formulation. The drug product specification includes tests for description, uniformity of dosage units, in vitro release profile, particle size distribution, pH, viscosity, identity, assay, impurities, osmolality, container closure integrity, polymorphic form, endotoxin, sterility, and redispersibility. The specification is acceptable. The proposed acceptance criteria for in vitro release profile is found acceptable by the biopharmaceutics reviewer Dr. Parnali Chatterjee. All analytical methods are described in reasonable detail and have been adequately validated.

The manufacturing process involves [(b) (4)] Batch analyses are provided for 4 batches (3 primary stability batches with [(b) (4)] vials and 1 batches with [(b) (4)] vials) manufactured by AMRI commercial manufacturing site. The revised commercial scale is [(b) (4)] vials. All batches complied with the proposed specification.

The long term, intermediate and accelerated stability data indicate the proposed drug product is stable at the recommended labeling storage condition. There are no obvious trends observed when stored at 25°C/60%RH for up to 24 months, 30°C/65%RH for 12 months, and 40°C/75%RH for 6 months. In addition, statistical analysis performed projects a shelf life of at least 30 months. No significant leachables were observed in the long-term stability (24 months) and intermediate stability samples (12 months). The applicant has provided freeze - thaw stability studies to indicate that the product is stable for transportation between -20°C and 40°C. The proposed expiration dating period of 24 months with the storage statement "Stored at 20°C to 25°C" is found acceptable.

The applicant provided a claim for a categorical exclusion from the preparation of an environmental assessment report as per 21 CFR §25.31 (b) and §25.15(a). The required statement of no extraordinary circumstances was included. The provided information was reviewed and the claim for categorical exclusion was found to be acceptable.

A pre-approval inspection (PAI) for (b) (4) was conducted to support the (b) (4) and the outcome of the PAI found the facility to be acceptable. All the other sites are adequate based on the manufacturing capabilities and inspection history. Therefore, OPF has provided an overall recommendation of "Approval" (see report dated 11/29/2017 in Panorama).

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[3]	H	Formulation includes (b) (4) (b) (4) sterilization has been validated; facilities were currently **"Acceptable"**.	L	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	H	Intraocular injection. Endotoxin testing is included in the specification.	L	
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.	L	
Assay (preservative)	Formulation Container closure[1] Process parameters Scale/equipment	L	No preserve in the formulation	L	

Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	M	2 mL Type glass vial with 0.5 mL fill volume. Deliver 0.005 mL for each single dose.	L	
pH	Formulation Container closure[1] Process parameters Scale/equipment	L	No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	Formulation Container closure[1] Process parameters Scale/equipment	L	The proposed drug product is a suspension and particle size distribution is included in the drug	L	
Extractables/leachables	Formulation Container closure	M	No significant extractable and leachables observed for 24 months at long term storage condition.	L	

1 Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.
2 Post-approval stability protocol provides for testing of 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 208912

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QUALITY ASSESSMENT
Chapter VII-Biopharmaceutics

BIOPHARMACEUTICS

NDA: 208912
Drug Product Name / Strength: Dexycu™ (Dexamethasone Suspension for Intraocular Injection, 9%)
Route of Administration: Intraocular Injection
Applicant Name: Icon Bioscience, Inc.

Background: Icon Bioscience, Inc. is seeking approval for Dexycu™ (Dexamethasone Suspension for Intraocular Injection, 9%) a sterile non-aqueous suspension of (b) (4) dexamethasone in acetyl triethyl citrate (ATEC) in prefilled 2 mL glass vial to be administered as a 5 µL injection into the (b) (4) of the eye for the treatment of postoperative inflammation following cataract surgery *via* the 505(b)(2) path. The listed drug was first identified on 4/12/2017 in Form 356h as Maxidex® (approved under NDA 13422), however, on form 356h submitted on 6/5/2017 both Maxidex® and Decadron® (approved under NDA 13422 and NDA 11984, respectively) were identified as the LDs, and subsequently on 6/8/2017 (in response to an FDA phone call) the listed drugs were identified as Decadron® Injection and Decadron® Solution drops (approved under NDA 12071 and NDA 11984, respectively). The Applicant relies, in part, on the existing safety information for dexamethasone available for the listed drugs. As a result, the Applicant conducted only limited non-clinical studies in rabbits, which was agreed upon during the pre-IND meetings. The Applicant stated that even if all dexamethasone (b) (4) in the proposed drug product were to be absorbed immediately following intraocular injection (which does not happen), total systemic exposures would be estimated to be 0.1 µg/mL (b) (4) well below levels detected after oral, intravenous and topical ocular administration.

In the current submission, the Applicant conducted two (2) Phase III clinical studies (C13-04 and C15-01) to assess the safety, efficacy, and the pharmacokinetic (PK) profile of the proposed drug product. Study C13-04 used batch no. 10090-005/13J001 manufactured at (b) (4) and study C15-01 used drug product batch no. 504-501-003 manufactured at the proposed commercial drug product manufacturing site, AMRI. The two studies indicated that both drug products exhibit low, dose-proportional, systemic exposure of dexamethasone. Furthermore, the in vitro release profiles for the batch no. 10090-005/13J001 manufactured at (b) (4) is similar to batch no. 504-501-003 that was manufactured at AMRI, with similarity factor '*f2*' value (b) (4), indicating that the two batches have similar in vitro release profiles.

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated **1)** the proposed in vitro release method, **2)** the proposed in vitro release acceptance criteria, and **3)** the need for bridging of the formulations throughout the product development process and across manufacturing site changes.

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

1) ***Proposed In Vitro Release Method:*** The proposed in vitro release method described below is acceptable for the batch release and stability testing of the proposed drug product.

ACCEPTABLE In Vitro Release Method for Dexamethasone Suspension for Intraocular Injection, 9%	
Parameters	Method
Apparatus/Speed	PION μDISS Profiler dissolution apparatus/with no agitation
Media/Volume	0.9% Sodium Chloride (saline) with 0.0005% Benzalkonium Chloride (BAC)/ 20 mL
Bath temperature	37.0±0.5°C
Sampling Time Points	Day 1, Day 3, Day 7, and Day 14
Sample volume and seeding location	5 μL/Center

2) ***Proposed In Vitro Release Acceptance Criteria***:

The in vitro release acceptance criteria of NMT (b)(4)% for Day 1, report results for Day 3, (b)(4)% for Day 7, and NLT (b)(4)% for Day 14 as proposed by the Applicant are permissive. The in vitro drug release data at batch release and during stability testing for the bio-batch (504-501-003) and two other registration batches (504-501-001 and 504-501-002) for the proposed Dexycu™ (Dexamethasone Suspension for Intraocular Injection, 9%) product supports narrower release acceptance criteria. In an Information Request comment the Applicant was recommended to implement in vitro release acceptance criteria of (b)(4)% at Day 1, (b)(4)% at Day 3, (b)(4)% at Day 7, and NLT (b)(4)% at Day 14 for the drug product. In response to the Information request, the Applicant propo ed new in vitro release acceptance criteria of (b)(4)% at Day 1, (b)(4)% at Day 3, (b)(4)% at Day 7, and NLT (b)(4)% at Day 14 for the drug product, which are permissive. During a teleconference between FDA and the Applicant on 12/12/2017, the Applicant agreed to the FDA recommended in vitro release acceptance criteria of (b)(4)% at Day 1, (b)(4)% at Day 3, (b)(4)-(b)(4)% at Day 7, and NLT (b)(4)% at Day 14.

Time	Applicant's Originally Proposed In Vitro Release Acceptance Criteria	Applicant's Newly Proposed In Vitro Release Acceptance Criteria	FDA Recommended and Final agreed upon In Vitro Release Acceptance Criteria
	% Dexamethasone Released	% Dexamethasone Released	% Dexamethasone Released
1 Day 3 Day 7 Day 14 Day	NMT (b) (4)% Report Results (b) (4)% NLT (b) (4)%	(b) (4)% (b) (4)% (b) (4)% Mean NLT (b) (4)%	(b) (4) % (b) (4)% (b) (4)% NLT (b) (4)%

3) ***Need for Bridging:***

The Applicant conducted two Phase 3 multi-center safety and efficacy studies, Study C13-04 (using drug product batch no. 10090-005/13J001 manufactured at (b) (4) and Study C15-01 (using drug product batch no. 504-501-003 manufactured at the proposed commercial site, AMRI). The results of the pharmacokinetics (PK) analysis from Study C13-04 and Study C15-01 (Phase 3, prospective, double-masked, placebo-controlled, parallel-design multi-center study) indicate that dexamethasone exhibits low, dose-proportional, systemic exposure in both treatment groups (reviewed by OCP). Since, the drug product manufactured at both manufacturing sites are used in the pivotal clinical studies, there is no need for bridging the drug products manufactured at the two sites. Nevertheless, the Applicant provided in vitro release data for the batch no. 10090-005/13J001 manufactured at (b) (4) and the batch no. 504-501-003 that was manufactured at AMRI using the proposed IVRT method with saline and 0.0005% BAC as the release media. The in vitro release profile for the batch no. 10090-005/13J001 manufactured at (b) (4) is similar to the in vitro release profile for batch no. 504-501-003 that was manufactured at the commercial site, AMRI with similarity factor '*f2*' value >50.

➢ ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 208912 for Dexycu™ **(**Dexamethasone Suspension for Intraocular Injection, 9%), is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:
Parnali Chatterjee, PhD ***12/18/2017***

Secondary Biopharmaceutics Reviewer Name and Date:
I concur with Dr. Chatterjee's assessment and recommendation.
Elsbeth Chikhale, PhD ***12/18/2017***

***OVERALL BIOPHARMACEUTICS RECOMMENDATION*:**

Based on the review of the overall information, from the Biopharmaceutics perspective NDA 208912 for Dexycu™ (Dexamethasone Suspension for Intraocular Injection, 9%) is recommended for **APPROVAL.**

BIOPHARMACEUTICS ASSESSMENT

- **LIST SUBMISSIONS BEING REVIEWED:**

Submissions Reviewed	Reference ID
Original NDA Submission: 208912-ORIG-1	\\cdsesub1\evsprod\nda208912\0001\m1\us\cover-letters.pdf
Response to Information Request Comment #1	\\cdsesub1\evsprod\nda208912\0021\m1\us\111-information-amendment\1111-information-amend-quality.pdf **(SDN 21)**
Response to Information Request Comment #2	\\cdsesub1\evsprod\nda208912\0023\m1\us\111-information-amendment\1111-quality-information-amend.pdf **(SDN 23)**
Response to Information Request Comment #3	\\cdsesub1\evsprod\nda208912\0024\m1\us\111-information-amendment\1111-quality-information-amend-biopharmaceutics.pdf **(SDN 24)**
Response to Teleconference held 12/12/2017	\\cdsesub1\evsprod\nda208912\0027\m1\us\12-cover-letters\cover-letter.pdf **(SDN 27)**

- ***DRUG PRODUCT*:**

In the current submission, the Applicant developed a controlled-release drug product, Dexycu™ (IBI-10090), which is a sterile, non-aqueous suspension containing 51.7 mg (b) (4) dexamethasone (9% w/w), USP, drug substance suspended in acetyl triethyl citrate (ATEC), NF, in 2 mL glass vial containing 0.5 mL drug product per vial. Each vial is packaged along with a syringe assembly for administration of the drug product. The syringe kit is designed to deliver 517 μg dexamethasone per 5 μL of the dose to be administered following completion of cataract surgery for the treatment of post-operative inflammation.

(b) (4)

(b) (4)

The qualitative and quantitative composition of the proposed To-Be-Marketed (TBM) drug product is shown in **Table I**. The proposed drug product is formulated with two ingredients, 9% w/w dexamethasone, the active pharmaceutical ingredient (API) and acetyl triethyl citrate (ATEC), (b) (4) (b) (4)

Table I. Qualitative and Quantitative Composition of Dexycu™, (Dexamethasone Suspension for Intraocular Injection, 9%) in 0.5 mL Vial

Ingredient	Function	Quality Standard	Amount (g/0.575g Vial Fill Weight)[a]	Amount (µg per 5 µL Intraocular Injection, DDS)[a,c]	Amount (wt %)
Formulation:					
Dexamethasone (b) (4)	Drug substance	USP	0.0517	517	9.0
Acetyl Triethyl Citrate (ATEC)	(b) (4)	NF	(b) (4)		
(b) (4)		NF	----	----	----
Total			(b) (4)		

[a] Based on drug product density of (b) (4)
[b] (b) (4)
[c] (b) (4) injected by syringe supplied in the administration syringe kit assembly

The composition of the various drug product batches that were manufactured during the product development stage are highlighted in **Table II.** Most of the preclinical and clinical studies for the proposed drug product were conducted with batches that were manufactured at (b) (4) ((b) (4) as shown in **Table IIIa and Table IIIb**. Five additional batches of the proposed drug product were manufactured at the proposed commercial manufacturing site, AMRI and used as primary and supportive stability batches containing 9%

w/w (b) (4) dexamethasone (see **Table IIIb)**. The Applicant conducted in vivo efficacy studies with batch no. 10090-005/13J001 manufactured at (b) (4) and the batch no. 504-501-003 that was manufactured at the proposed commercial site, AMRI.

Table II. Composition of the Various Drug Product Batches with Different Strengths Manufactured During Product Development

Ingredient	1% 004/09I001 Amount (wt %)	4.5% 001/09A001 Amount (wt %)	6% 002/09A001, 002/10E001 Amount (wt %)	9% 005/10E001, 005/13J001 Amount (wt %)	9% 504-501-003 Amount (wt %)	12% 006/10E001 Amount (wt %)
Formulation						
Dexamethasone (b) (4) USP	(b) (4)					
Acetyl Triethyl Citrate (ATEC), NF						(b) (4)
Total	100	100	100	100	100	100

Table IIIa. Different Batches of the Proposed Drug Product that were Manufactured at original manufacturing site (b) (4) and the proposed commercial manufacturing site AMRI used in Different Clinical Studies

Study No. / Commercial	Phase	Mfg. Site	IBI-10090 Batch No. (Concentration)	Total Dose/ Injection Volume	Syringe Delivery System[a]	Ref. Section 2.3.P.5
Preclinical Tox Study 09C0010G-X01G	0	(b) (4)	(b) (4)			
Clinical Study C09-01	2					
Clinical Study C10-01	2					
Clinical Study C11-01	2					

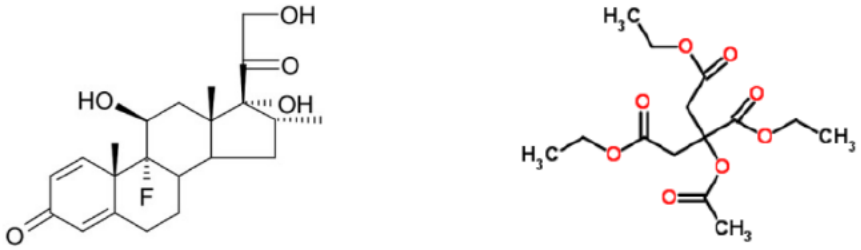
Table IIIa-continued. Different Batches of the Proposed Drug Product with Different Strengths that were Manufactured at (b) (4) and AMRI Manufacturing Sites and used in Different Clinical Studies

Study No. / Commercial	Phase	Mfg. Site	IBI-10090 Batch No. (Concentration)	Total Dose/ Injection Volume	Syringe Delivery System[a]	Ref. Section 2.3.P.5
Clinical Study C13-04	3	(b) (4)	10090-003/13I001 (0%)	0 µg/5 µL		(b) (4)
			10090-002/13I001 (6%)	342 µg/5 µL		
			10090-005/13J001 (9%)	517 µg/5 µL		
Clinical Study C15-01	3		504-501-003 (9%)	517 µg/5 µL		
Commercial	Post-approval		Commercial batches (9%)	517 µg/5 µL		

(b) (4)

BCS DESIGNATION

Since this drug product is administered as an ocular injection, a BCS designation is not applicable. The active ingredient in the proposed drug product is (b) (4) dexamethasone, USP ($C_{22}H_{29}FO_5$, molecular weight=392.46, see **Figure II**), a synthetic glucocorticoid. (b) (4) dexamethasone is white to practically white, odorless, (b) (4) powder with (b) (4)



Panel A **Panel B**

Figure II. Chemical Structure of Dexamethasone **(Panel A)** and ATEC **(Panel B)**

- ***Solubility:*** (b) (4)

Table IV. Solubility Profile of Dexamethasone in Organic Solvents

Solvent	Solubility (USP)
(b) (4)	

- ***Permeability:*** The current submission does not include any in vitro permeability data. However, the Applicant conducted two Phase 3 multi-center safety and efficacy studies. The results of the pharmacokinetics (PK) analysis from clinical studies **C13-04** and **C15-01** (Phase 3, prospective, double-masked, placebo-controlled, parallel-design multi-center study) which were conducted to evaluate the safety and efficacy of a single-dose of the proposed Dexycu™ drug product for batches manufactured at (b) (4) and the proposed commercial site, AMRI (517 µg/5 µL of 9% w/w (b) (4) dexamethasone) indicated that dexamethasone exhibits low, dose-proportional, systemic exposure after intraocular injection in both treatment groups. Dexamethasone plasma concentration declined over time in most patients, with measurable concentrations observable only in a few patients on Day 15, post-operatively.

➢ ***IN VITRO RELEASE TESTING (IVRT) INFORMATION:***

Because in vitro release testing (IVRT) is a critical quality attribute, the Applicant utilized the IVRT method throughout the drug product development process for testing batches used in the clinical PK studies and stability studies. Furthermore, the IVRT was utilized to bridge formulations produced at different manufacturing sites and process changes during the formulation development phase. In addition, the Applicant provided IVRT data to demonstrate the robustness of the IVRT method and its ability to discriminate drug products that were intentionally manufactured with meaningful aberrations.

➢ ***PROPOSED IVRT METHOD:***

The IVRT method and in vitro release acceptance criteria proposed by the Applicant for the proposed drug product are presented below, in **Table V**.

Table V. Proposed IVRT Method and originally proposed In Vitro Release Acceptance Criteria

Parameters	Method
Apparatus/Speed	PION μDISS Profiler dissolution apparatus/no agitation
Media/Volume	0.9% Sodium Chloride with 0.0005% Benzalkonium Chloride (BAC)/20 mL
Bath temperature	37.0±0.5°C/20 mL
Sampling Time Points	Day 1, Day 3, Day 7, and Day 14
Sample Volume	5 μL
Seeding position	Center
Analytical Method	HPLC/UV at 240 nm
Originally Proposed In Vitro Release Acceptance Criteria	Time % Dexamethasone Released
	1 Day NMT (b) (4)% 3 Day Repo results 7 Day (b) (4)% 14 Day NLT (b) (4)%

REVIEWER'S ASSESSMENT *for the Proposed IVRT Method:*

- ***Dissolution Apparatus and Agitation Speed:***

(b) (4)

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Table IXb. In Vitro Release Data for the Bio-batch 504-501-003 Manufactured at AMRI and Two Registration Batches (504-501-001 and 504-501-002) Manufactured at AMRI and tested at Icon and AMRI using the Proposed IVRT Method (saline containing 0.0005% BAC)

Batch 504-501-001					
Testing Site/f2	Icon	AMRI	AMRI	f2	f2
Day	Mean (%)[a] Section 3.2.P.2.2	Mean (%)[a] 18M	Mean (%)[a] 24M	3.2.P.2.2 vs. 18M	3.2.P.2.2 vs. 24M
1	30.5	23.3	22.2	52	64
3	51.6	40.5	51.1		
7	76.9	65.1	78.8		
14	91.2	90.1	96.3		
Batch 504-501-002					
Day	Mean (%)[a] Section 3.2.P.2.2	Mean (%)[a] 18M	Mean (%)[a] 24M	f2 3.2.P.2.2 vs. 18M	f2 3.2.P.2.2 vs. 24M
1	31.8	22.1	20.2	52	57
3	51.9	41.2	44.5		
7	79.3	68.5	75.4		
14	92.7	93.8	95.5		
Batch 504-501-003					
Day	Mean (%)[a] Section 3.2.P.2.2	Mean (%)[a] 18M	Mean (%)[a] 24M	f2 3.2.P.2.2 vs. 18M	f2 3.2.P.2.2 vs. 24M
1	30.4	24.2	24.5	67	62
3	48.4	46.9	52.8		
7	71.2	76.2	79.7		
14	93.6	96.8	95.7		

[a] Mean of 12 units

In response to the Information Request, the Applicant proposed the following new in vitro release criteria for the drug product on 12/05/2017:

Time	Applicant's Initially Proposed In Vitro Release Acceptance Criteria % Dexamethasone Released	FDA Recommended In Vitro Release Acceptance Criteria % Dexamethasone Released	Applicant's Newly Proposed In Vitro Release Acceptance Criteria % Dexamethasone Released
1 Day	NMT (b) (4)%	(b) (4) %	(b) (4) %
3 Day	Report results	%	%
7 Day	(b) (4) %	%	%
14 Day	NLT (b) (4) %	NLT (b) (4)%	Mean NLT (b) (4) %

The Applicant noted that based on the 18 month and 24 month stability data for the bio-batch (504-501-003) and two other registration batches, some individual data points would not comply with the recommended in vitro release criteria for the drug product at Level 1. Therefore, the Applicant proposed the in vitro release acceptance criteria of (b) (4)% at Day 1, (b) (4)% at Day 3, (b) (4)% at Day 7, and NLT (b) (4)% at Day 14 for the drug product. However, the current FDA practice is to set release acceptance criteria based on Level 2 (n=12), using the mean drug release and +/- 10% as ranges. Based on the release data for the bio-batches and the registration batches, the FDA recommended in vitro release specifications were agreed upon by the Applicant in a Teleconference held with the Applicant on 12/12/2017. In addition, the Applicant updated the batch release specifications with the FDA recommended in vitro release criteria for the drug product in the Section 2.3. P.5, 2.3.P.8, 3.2.P.5.1, 3.2.P.5.4, 3.2.P.5.6, and the stability protocol and stability specifications in the Section 3.2.P.8.1, and 3.2.P.8.3.

- ***BRIDGING OF FORMULATIONS DUE TO MANUFACTURING SITE CHANGES:***

Preclinical and early Phase I and Phase II clinical studies for the proposed drug product were conducted with batches containing 4.5%, 6%, 9% and 12% w/w (b) (4) dexamethasone that were manufactured at (b) (4) as shown in **Table IIIa and Table IIIb**. The Applicant manufactured an additional five batches containing 9% w/w (b) (4) dexamethasone (see **Table IIIb)** to be used as primary and supportive stability batches at the commercial manufacturing site, AMRI. The manufacturing site change from (b) (4) to AMRI includes changes in the (b) (4) (see **Table X**). These changes would qualify as SUPAC Level 3 changes and therefore, the Applicant conducted two Phase 3 clinical studies **C13-04** (using (b) (4) batch 10090-005/13J001) and **C15-01** (using batch 504-501-003 that was manufactured at the proposed commercial manufacturing site, AMRI) containing the same formulation, 517 µg/5 µL of 9% w/w (b) (4) dexamethasone. Since, the drug product

manufactured at both manufacturing sites are used in the pivotal clinical studies, there is no need for bridging drug products manufactured at the two sites.

Nevertheless, the Applicant provided in vitro release data for batch no. 10090-005/13J001 manufactured at (b) (4) and batch no. 504-501-003 that was manufactured at proposed commercial manufacturing site, AMRI (see **Table IXa** and **IXb**) containing the same formulation, 517 µg/5 µL of 9% w/w (b) (4) dexamethasone using the proposed IVRT method with saline and 0.0005% BAC as the release media. From **Table IXa** and **IXb** it can be concluded that the in vitro release profile for batch no. 10090-005/13J001 manufactured at (b) (4) is similar to the in vitro release profile for batch no. 504-501-003 that was manufactured at AMRI, with similarity factor '*f2*' value >50.

Table X. Manufacturing Site, Batch Size, and Process Changes for the Proposed Drug Product

- ***PK data on the clinical batches manufactured at (b) (4) and AMRI:***

The results of the pharmacokinetics (PK) analysis (see **Table XI**) from Study C13-04 and Study C15-01 (Phase 3, prospective, double-masked, placebo-controlled, parallel-design multi-center study) containing the same formulation, 517 µg/5 µL of 9% w/w (b) (4) dexamethasone indicate that dexamethasone exhibits low systemic exposure in both treatment groups. The T_{max} for both the batches are similar at 1 hour, however, the AUC_{0-t} for dexamethasone from batch no. 504-501-003 manufactured at the proposed commercial manufacturing site, AMRI, is twice that of the batch no. 10090-005/13J001 manufactured at (b) (4) The clinical pharmacology data will be reviewed by OCP.

Table XI. Pharmacokinetics Analysis of Dexamethasone from the Bio-batch (504-501-003) Manufactured at AMRI and Batch no. 10090-005/13J001 Manufactured at (b) (4)

Study Identifier	Product ID/ Batch No.	Study Objective/PK Analysis Objective	Treatments and Route	PK Population (M/F)	Mean Age (Range)	Dexamethasone Pharmacokinetic Parameters[a]			
						C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} [b] (hr•ng/mL)	AUC_{0-inf} (hr•ng/mL)
C13-04	IBI-10090 Batch: 10090-003/13I001 (0%) 10090-002/13I001 (6%) 10090-005/13J001 (9%)	To evaluate the efficacy and safety of two dose groups of IBI-10090 in the treatment of inflammation associated with cataract surgery. To determine dexamethasone PK parameters for a subgroup of patients (n=25).	Placebo	4 (2M/2F)	73.8 (62-80)	0	0	0	0
			1 x IBI-10090 342 mcg	13 (7M/6F)	70.0 (57-81)	0.380 (0.1997)	1.301 (0.8167)	1.028 (0.7651)	- [c]
			1 x IBI-10090 517 mcg	8 (4M/4F)	69.3 (56-87)	0.536 (0.3652)	1.016 (0.1399)	2.210 (2.1245)	5.605 (3.0400)
			A single 5-mcl dose administered by intraocular injection						
C15-01	IBI-10090 Batch 504-501-003	To evaluate the safety of a single dose of IBI-10090 in the treatment of inflammation associated with cataract surgery. To determine dexamethasone PK parameters for a subgroup of patients (n=13).	1 x IBI-10090 517 mcg	13 (5M/8F)	68.2 (40-78)	0.735 (0.701)	1.00 (0.000)	4.64 (10.1)	- [b]
			A single 5-mcl dose administered by intraocular injection						

Source: Table 1, Table 2 and Table 3 in this Summary of Clinical Pharmacology

[a] Arithmetic mean ± standard deviation

[b] AUC_{0-t}: the final time point in Study C13-04 was POD 15, while the final time point in Study C15-01 was POD 30

[c] AUC_{0-inf} could not be estimated

- ***POST-APPROVAL COMMITMENTS:*** **None**
- ***LIST OF DEFICIENCIES:*** **None**
- ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 208912 for Dexycu™ (Dexamethasone Suspension for Intraocular Injection, 9%) is recommended for **APPROVAL**.

APPENDIX I

INFORMATION REQUESTS TO THE APPLICANT AND APPLICANT'S RESPONSES:

I. *Biopharmaceutics Comments Conveyed to the Applicant on November 13, 2017:*

1. In the Module 2.3.P.5 for Control of Drug Product it is noted that you have proposed the in vitro release acceptance criteria for the Dexamethasone Suspension for Intraocular Injection, 9% drug product based on two different in vitro release methods. We recommend that you propose the in vitro release acceptance criteria based on the in vitro release data for the bio-batch 504-501-003 and if available two other registration batches (batch number 504-501-001 and 504-501-002) of Dexamethasone Suspension for Intraocular Injection, 9% drug product manufactured at AMRI site using the proposed in vitro release method with saline containing 0.0005% benzalkonium chloride as the release medium.

2. In order to set meaningful in vitro release acceptance criteria, we request that you provide complete in vitro release data for 12 dosage units (individual, mean, ranges, and % CV) across all time-points (up to 21 days) generated using the proposed in vitro release method using saline containing 0.0005% benzalkonium chloride as the release medium for the bio-batch 504-501-003 and if available two other registration batches of Dexamethasone Suspension for Intraocular Injection, 9% drug product manufactured at AMRI.

The Applicant responded to the Information Request #I comments on November 16, 2017, SDN (21)

(Refer to: \\cdsesub1\evsprod\nda208912\0021\m1\us\12-cover-letters\cover-letter.pdf)

1. In the Module 2.3.P.5 for Control of Drug Product it is noted that you have proposed the in vitro release acceptance criteria for the Dexamethasone Suspension for Intraocular Injection, 9% drug product based on two different in vitro release methods. We recommend that you propose the in vitro release acceptance criteria based on the in vitro release data for the bio-batch 504-501-003 and if available two other registration batches (batch number 504-501-001 and 504-501-002) of Dexamethasone Suspension for Intraocular Injection, 9% drug product manufactured at AMRI site using the proposed in vitro release method with saline containing 0.0005% benzalkonium chloride as the release medium.

Sponsor Response

Icon agrees with the Agency that the proposed in vitro release dissolution method TM.04797 with dissolution medium containing saline and 0.0005% benzalkonium chloride (saline/BAC) is the commercial release method as listed in Table 1 Section 2.3.P.5.1.1.1. This method has been developed in response to the Agency's request from the December 3, 2015 pre-NDA Type B meeting for providing more robust dissolution conditions. Since its

(b) (4)

[redacted]

2. In order to set meaningful in vitro release acceptance criteria, we request that you provide complete in vitro release data for 12 dosage units (individual, mean, ranges, and % CV) across all time-points (up to 21 days) generated using the proposed in vitro release method using saline containing 0.0005% benzalkonium chloride as the release medium for the bio-batch 504-501-003 and if available two other registration batches of Dexamethasone Suspension for Intraocular Injection, 9% drug product manufactured at AMRI.

Sponsor Response

Copies of individual in vitro release dissolution reports for 12 units (individual, mean, ranges, and % RSD) are attached to this response. A summary of AMRI batches, stability schedule, vial orientation, and storage conditions are provided Table 2. Also, as noted in Table 1, justification for the saline/BAC in vitro dissolution acceptance criteria (see Table 3) is primarily based on cumulative release and stability data from registration batches (504-501-003, 504-501-002 and 504-501-001) and engineering batch (504-501-ENG-003) that were stored at long-term and accelerated storage conditions in upright and/or inverted vial orientations as described in Module 3 Table 12, Section 3.2.P.5.6.1. The table will be updated as more data from stability programs become available. Dissolution data in saline/BAC dissolution medium has been gathered for up to 14 days, the late stage of the dissolution profile, which provides complete release of dexamethasone (b) (4)

Table 2 List of Batches and Conditions That Were Tested Using In Vitro Saline/BAC Release Dissolution Method TM.04797

Batch Number	Stability Schedule (in month)	Vial Orientation	Storage Condition
504-501-003	18 and 24	Inverted and Upright	25°C/60%RH
504-501-001	18 and 24	Inverted only[a]	25°C/60%RH
504-501-002	18 and 24	Inverted and Upright	25°C/60%RH
504-501-ENG-003	0, 1, 2, 3, 6, 9 and 12	Inverted	25°C/60%RH
504-501-ENG-003	0, 1, 2, 3 and 6	Inverted	40°C/75%RH

[a] Insufficient number of vials left for upright testing

Table 3 Proposed Specification Acceptance Criteria for In Vitro Release Dissolution Method in Saline/BAC (TM.04797) – Excerpt from Section 3.2.P.5.1

Test Parameter	Analytical Method	Current Acceptance Criteria
In Vitro Cumulative Release Profile 1 Day 3 Day 7 Day 14 Day	TM.04797	 Mean NMT (b) (4)% Report mean result (b) (4) Mean % Mean NLT (b) (4)%

II. ***Biopharmaceutics Comments Conveyed to the Applicant on November 28, 2017:***

1. Explain the difference in the in vitro release data for the registration batches (504-501-001,504-501-002, and 504-501-003) noted in Table 27 of the Drug Product document Module 3.2.P.2.2 and the 18 months and 24 months stability data for these batches provided in your amendment dated 11/21/2017.
2. (b) (4)
3. Provide the age and storage condition for batch IBI-005-13J001 and the registration batches (504-501-001, 504-501-002, and 504-501-003) at the time of the in vitro release testing shown in Figure 40 (batch IBI-005-13J001) and Table 27 (all 4 batches).
4. Provide the age range and storage condition for batch IBI-005-13J001 and batch 504-501-003 at the time these batches were used in the clinical studies C13-04 and C15-01.

The Applicant responded to the Information Request #II comments on November 30, 2017, SDN (23)

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Biopharmaceutics:

1. Explain the difference in the in vitro release data for the registration batches (504-501-001,504-501-002, and 504-501-003) noted in Table 27 of the Drug Product document Module 3.2.P.2.2 and the 18 months and 24 months stability data for these batches provided in your amendment dated 11/21/2017.

Sponsor Response

The in vitro release dissolution profiles for registration batches (504-501-001, 504-501-002 and 504-501-003) in saline/BAC dissolution medium (method TM.04797) meet the f2 value ≥ 50 (range 50-100) for the data reported in Section 3.2.P.2.2 Table 27 and the 18 months and 24 months stability data provided in the SN0021 amendment dated 11/13/2017 (cited amendment dated 11/21/2017 references SN0022). Data are summarized in Table 1. It should be noted that the testing for the data reported in Section 3.2.P.2.2 Table 27 was performed at Icon Bioscience while the stability testing (18 months and 24 months) was performed at AMRI, the commercial testing site. All f2 results are between 50 and 100, which ensures equivalence (sameness) of the two curves generated at two different testing sites. In addition, all dissolution results conform to the proposed commercial dissolution acceptance criteria described in Section 3.2.P.5.1.

The results demonstrate that the in vitro dissolution profiles from Table 27 of the Drug Product document Module 3.2.P.2.2 and 18 and 24 months stability samples are not statistically different.

Table 1 **Comparison of In-Vitro Release in Saline/BAC and f2 Similarity Factor Data from Section 3.2.P.2.2 and Registration Stability Program (ref. IR Dated November 13, 2017, SN0021) for Batches 504-501-001, 504-501-002 and 504-501-003**

Batch 504-501-001					
Testing Site/f2	Icon	AMRI	AMRI	f2	f2
Day	Mean (%)[a] Section 3.2.P.2.2	Mean (%)[a] 18M	Mean (%)[a] 24M	3.2.P.2.2 vs. 18M	3.2.P.2.2 vs. 24M
1	30.5	23.3	22.2	52	64
3	51.6	40.5	51.1		
7	76.9	65.1	78.8		
14	91.2	90.1	96.3		
Batch 504-501-002					
Day	Mean (%)[a] Section 3.2.P.2.2	Mean (%)[a] 18M	Mean (%)[a] 24M	f2 3.2.P.2.2 vs. 18M	f2 3.2.P.2.2 vs. 24M
1	31.8	22.1	20.2	52	57
3	51.9	41.2	44.5		
7	79.3	68.5	75.4		
14	92.7	93.8	95.5		
Batch 504-501-003					
Day	Mean (%)[a] Section 3.2.P.2.2	Mean (%)[a] 18M	Mean (%)[a] 24M	f2 3.2.P.2.2 vs. 18M	f2 3.2.P.2.2 vs. 24M
1	30.4	24.2	24.5	67	62
3	48.4	46.9	52.8		
7	71.2	76.2	79.7		
14	93.6	96.8	95.7		

[a] Mean of 12 units

(b) (4)

both studies conform to the proposed commercial dissolution acceptance criteria described in Section 3.2.P.5.1.

(b) (4)

3. Provide the age and storage condition for batch IBI-005-13J001 and the registration batches (504-501-001, 504-501-002, and 504-501-003) at the time of the in vitro release testing shown in Figure 40 (batch IBI-005-13J001) and Table 27 (all 4 batches).

Sponsor Response

The requested information is summarized in Table 3.

Table 3 Summary Information for Q3

Batch	IBI-005-13J001	504-501-001	504-501-002	504-501-003
Approx. Age in Months (Section 3.2.P.2.2, Figure 40)	28	N/A	N/A	N/A
Approx. Age in Months (Section 3.2.P.2.2, Table 27)	32	21	20	20
Storage Condition in Testing Laboratory[a]	Maintained within CRT (15 to 30°C)	Maintained within CRT (15 to 30°C)	Maintained within CRT (15 to 30°C)	Maintained within CRT (15 to 30°C)

[a] Laboratory temperature maintained and recorded at the time of testing within the controlled room temperature range of 15 to 30°C

N/A Not applicable

4. Provide the age range and storage condition for batch IBI-005-13J001 and batch 504-501-003 at the time these batches were used in the clinical studies C13-04 and C15-01.

Sponsor Response

The requested information is summarized in Table 4.

Table 4 Summary Information for Q4

Batch	IBI-005-13J001	504-501-003
Clinical Study	**C13-04**	**C15-01**
Approx. Age in Months (First Subject)	2	13
Approx. Age in Months (Last Subject)	8	22
Storage Condition at Clinical Sites/Surgical Centers[a]	Maintained within CRT (15 to 30°C)	Maintained within CRT (15 to 30°C)

[a] Temperature prevalent in clinical sites/surgical centers maintained and recorded within the controlled room temperature range of 15 to 30°C

III. *Biopharmaceutics Comments Conveyed to the Applicant on December 1, 2017:*

1. Based on the provided in vitro release data for the clinical batches (005-13J001 and 504-501-003) and two other registration batches (504-501-001 and 504-501-002), the following in vitro release acceptance criteria for batch release and stability testing of the proposed Dexamethasone Suspension for Intraocular Injection, 9% drug product are recommended:

Recommended In Vitro Release Acceptance Criteria	Time	% Dexamethasone Released
	1 Day	(b) (4) %
	3 Day	%
	7 Day	%
	14 Day	NLT (b) (4) %

Note that the setting of in vitro release acceptance criteria is based on Level 2 testing (n=12), and therefore, in vitro release testing may sometimes require Level 2 testing and occasionally Level 3 testing.

2. Provide a copy of the revised specifications table for your drug product with the revised acceptance criteria for the in vitro release test. Also, update other sections of your submission as appropriate.

The Applicant responded to the Information Request #III comments on December 5, 2017, SDN (24)

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Sponsor Response

Icon Bioscience acknowledges the Agency's recommended In Vitro Release Acceptance Criteria and proposes a change to the recommended acceptance criteria for commercial dissolution method in saline/BAC. The proposed revised limits are summarized in Table 1 and take into consideration the following points:

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(b) (4)

[redacted]

2. Provide a copy of the revised specifications table for your drug product with the revised acceptance criteria for the in vitro release test. Also, update other sections of your submission as appropriate.

Sponsor Response

Upon receipt of the Agency's response to the specifications proposed in Question 1, Icon will revise the In Vitro Release Acceptance Criteria specification and corresponding Modules within the NDA 208912 for Dexycu (dexamethasone suspension for intraocular injection, 9%).

IV. *Applicant's Response to the CDER-Biopharmaceutics Teleconference Held with the Applicant on December 12, 2017 to address the In Vitro Release Acceptance Criteria for the Proposed Drug Product Dated 12/15/2017, SDN (27)*

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Reference is made to the December 1, 2017 CMC information request, which recommended new *in vitro* release acceptance criteria for released Dexamethasone and the sponsor's response submitted on December 5, 2017 (SN 0024) that proposed alternative acceptance criteria. Reference is also made to the December 12, 2017 teleconference between the FDA and the sponsor regarding the *in vitro* release acceptance criteria. On the teleconference, the sponsor agreed to the proposed *in vitro* release acceptance criteria proposed by the FDA on December 1, 2017.

The purpose of this submission is to update the *in vitro* release acceptance criteria in the Module 2 and Module 3 sections for released Dexamethasone per the FDA's recommendation. A summary of changes is provided in Module 1.11.1. This submission includes the following:

- Quality Overall Summary - Control of Drug Product (Module 2.3.P.5)
- Quality Overall Summary – Stability (Module 2.3.P.8)
- Specifications (Module 3.2.P.5.1)
- Batch Analyses (Module 3.2.P.5.4)
- Justification of Specifications (Module 3.2.P.5.6)
- Stability Summary and Conclusion (Module 3.2.P.8.1)
- Postapproval Stability Protocol and Stability Commitment (Module 3.2.P.8.2)
- Stability Data (Module 3.2.P.8.3)

APPEARS THIS WAY ON ORIGINAL

Parnali Chatterjee

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Elsbeth Chikhale

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Date: 12/18/2017 03:38:00PM
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QUALITY ASSESSMENT

MICROBIOLOGY

Product Background:

NDA: 208912

Drug Product Name / Strength: Dexycu intraocular injection, 9 % (0.5 mg dexamethasone/ 0.005 mL injection) 0.5 mL fill

Route of Administration: Intraocular injection

Applicant Name: Icon Bioscience, Inc.

Manufacturing Site: Albany Molecular Research, Inc. (AMRI Burlington, Inc.)
99 South Bedford Street, Burlington, MA 01803

Method of Sterilization: The drug product in the final container/ closure is (b) (4)

Review Recommendation: Adequate

Review Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
4/12/2017	4/12/2017	N/A	6/5/2017
10/17/2017	10/17/2017	N/A	10/19/2017
11/21/2017	11/21/2017	N/A	11/21/2017
12/01/2017	12/07/2017	N/A	12/07/2017

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: This is an eCTD submission. IR#1, IR#2, and IR#3 were conveyed to the applicant on 10/10/2017, 11/16/2017, and 12/1/2017 respectively. Response to IR#1 (received on 10/17/2017), IR#2 (received on 11/21/2017), and IR#3 (received on 12/07/2017) were incorporated in the review. The IR response received on 12/07/2017, included a commitment for submission of hold time studies for the batch size of (b) (4) units at a later time. It was indicated that an engineering batch run for a total of (b) (4) vials will commence on 12/11/2017, bioburden data will be collected (b) (4) will be submitted to the Agency in an NDA supplement prior to commercialization. This was acceptable by this reviewer following consultation and concurrence from Branch Chief (Acting), Bryan S. Riley, Ph.D. Please refer to Section P.3.5 of this review for additional information.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: Type V DMF # (b) (4) and associated microbiology reviews 11648mic24.doc (adequate; dated April 26, 2013) and 11648mic31.doc (adequate, dated August 25, 2015) regarding (b) (4)

List Number of Comparability Protocols (ANDA only): NA

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Dexycu intraocular injection is a sterile non-aqueous suspension of (b) (4) dexamethasone drug substance (USP) in acetyl triethyl citrate NF.
- **Drug product composition –**

Ingredient	Function	Quality Standard	Amount (g/0.575g vial Fill weight)[a]	Amount (µg per 5 µL Intraocular Injection, DDS)[a, c]	Amount (wt %)
Formulation					
Dexamethasone (b) (4)	Drug substance	USP	0.0517	517	9.0
Acetyl Triethyl Citrate (ATEC)	(b) (4)	NF	(b) (4)		
(b) (4)		NF	---	---	---
Total			(b) (4)		

[a] Based on drug product density of (b) (4)

[b] (b) (4)

[c] (b) (4) injected by syringe supplied in the administration syringe kit assembly

Exhibit batches:

Proposed commercial batch size of the drug product: (b) (4) kg (b) (4) vials)

Batch Type	Drug Product	Syringe Assembly Pouches
Exhibit batches	(b) (4) kg (b) (4) vials)	(b) (4) pouches
Proposed commercial batch	kg vials)	pouches

- **Description of container closure system**

Each single use vial is packaged in a kit with all of the components needed for administration of the drug.

The kit includes four individual sterile pouches containing the following:

- One syringe assembly (syringe ring and syringe guide)
- One commercially available syringe, 1 mL
- One commercially available syringe cannula, 25 G x 8 mm bend
- One commercially available syringe needle, 18 G x 11 ½

Container closure system for drug product (table reproduced from the submission)

Vial/Stopper/Cap Information	Supplier/Manufacturer	Supplier/Manufacturer Part Number	DMF Reference
[redacted] (b) (4)			

Note to the reviewer: The applicant states that the vials can also be supplied by [redacted] (b) (4) The glass material and dimensions are equivalent.

Administration Syringe Kit Assembly (table reproduced from the submission)

Sterile Pouch	Component	Manufacturer/ Supplier[a]	Manufacturer/ Supplier Part Number	Regulatory Reference
IBI-10090 Syringe Assembly	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4)
Syringe				
Syringe Cannula				
Syringe Needle				

[a] Commercially available except where noted

[b] Class I device, exempt from 510K premarket notification

IBI-10090 Syringe Guide and Snap-on Ring Assembled with Commercial Syringe with Affixed Cannula Needle (figure reproduced from the submission)

[redacted] (b) (4)

DEXYCY (IBI-10090) Market Package Assembly (figure reproduced from the

Reviewer's Assessment: ***Adequate***
The proposed container closure system and drug product composition were adequately described.

Based on the email conversation with Wiley A. Chambers, SUPV MEDICAL OFCR (OPHTAL), FDA/OMPT/CDER/OND/OAP/DTOP, via Chunchun Zhang, Chemist, FDA/OMPT/CDER/OPQ/ONDP/DNDPI/NDPBIII, this reviewer was advised that the syringe assembly components containing the syringe ring and guide was regulated as drugs if packaged with the drugs with which they are to be used (per 21 CFR 200.50; see excerpt inserted below*) and not as a device and that the product quality microbiology reviewer would cover the sterilization validation studies for these package assemblies. The sterilization validation studies of the, "IBI-10090 Syringe Assembly kit", was therefore covered by Division of Microbiology Assessment in this review. Refer to Section P.3.5 for additional information on these sterilization validation studies.

**21 CFR 200.50(c) states: "Eye cups, eye droppers, and other dispensers intended for ophthalmic use should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. These articles, which are regulated as drugs if packaged with the drugs with which they are to be used, should be packaged so as to maintain sterility until the package is opened and be labeled, on or within the retail package, so as to afford adequate directions and necessary warnings to minimize the hazard of injury resulting from contamination during use".*

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

All sterile components of the IBI-10090 Administration Syringe Kit Assembly except the IBI-10090 Syringe Assembly (pouch containing one syringe guide and one ring made under ISO 9001:2008 guidelines approved by (b) (4)) are sourced from

commercial suppliers with FDA 510K clearance (b) (4) or 510K exemption for class I device (b) (4)

Distribution simulation study of IBI-10090 market package was performed to ensure that the market package containing IBI-10090 vialed drug product and IBI-10090 Administration syringe kit assembly will protect its content from damage during post-sterilization handling and distribution. The market package was subjected to physical distribution and environmental stress testing. Additionally, visual test, bubble test, dye penetration under pressure differential test, and peel test were performed.

BI-10090 Administration Syringe Kit Assembly:
(3.2.P.7 Container Closure System.pdf; p18/26)

Validation method: The suitability of pouches to maintain sterility of the IBI-10090 Syringe Assembly components was confirmed by verification of the seal and pouch integrity (visual inspection, peel and bubble tests) and bacterial endotoxin tests after (b) (4). The focus of this review will be the bubble test method.

Bubble Test: ASTM F2096-11; Detecting Gross Leaks in Packaging by Internal Pressurization.
Test units: 90 pouches of IBI-10090 Syringe Assembly (ICO-004) were used for testing.

Brief description of Bubble Test: Samples were submerged one inch below the water surface and subjected to pressure of 0.35 psi.

Validation acceptance criteria:
No evidence of a steady stream of bubbles from sealed areas or from pinholes/ cuts in the packaging materials.

Results: No steady stream of bubbles were observed from the sealed areas or packaging materials.

IBI-10090 drug product vial
(3.2.P.7 Container Closure System.pdf; p19/26)

Validation method: Dye Penetration under Pressure Differential Testing (ASTM F3039-15, Detecting Seal Leaks in Nonporous Packaging or Flexible Barrier Materials and ASTMD6653, Determining the Effects of High Altitude on Packaging Systems by Vacuum method). This method has also been used for stability studies.

The test method ASTMF3039-15 provides attribute data on the integrity of the primary package directly after production or after experiencing a dynamic or environmental related event. It may be used to visually identify a leak through a channel as small as 0.002" in the seal area.

The test method ASTMD6653 determines the effects of pressure differential when packaged products are transported via certain modes of transport, such as feeder aircraft or ground over high mountain passes. The results of these tests are intended to be used for qualitative purpose.

Test units:

- 30 test vials and one positive control vial were used in the test.
- Vial not immersed in dye solution was used as the negative control.

Brief description of dye penetration under pressure differential test method:

- 30 Test and positive control vials were placed upright in a container and completely submerged in the dye solution. The container with dye solution and samples were placed inside a vacuum chamber and the external pressure was reduced to 12.0 in. Hg. Samples were allowed to stand for 60 mins at the reduced external pressure.
- The samples were removed from the container and rinsed with purified water and wiped using a disposable wipe.
- The packaging of each sample was agitated by inverting several times. Each sample was visually compared to a negative control, which was not immersed in dye solution, on a white background to determine if there is an indication that the dye solution entered the vial. A blue color inside the packaging as compared to the negative control sample is indicative that dye has entered the packaging. The process was repeated for each positive control and sample group.

Note to the reviewer: Total number of positive control and the criteria for a positive control was not provided. Additionally, the type of dye and concentration of dye solution used is unclear. Information is requested below.

Validation acceptance criteria:

- No evidence of dye penetration into the vial.

Results:

- The applicant indicates that their acceptance criteria were met.
- All test vials showed no evidence of dye penetration. Data for positive control and negative control was not provided, additional information is requested below.

The following information request was conveyed to the applicant on 10/10/2017 and the response was received on 10/17/2017.

IR:

Regarding container closure integrity testing using dye immersion:

(a) Please clarify if all the test units and positive control were subjected to the maximum [redacted] (b) (4) *sterilization conditions prior to container closure integrity testing.*

Applicant's response: The applicant confirmed that all the test units and positive control were subjected to a validated [redacted] (b) (4) sterilization process prior to container closure integrity testing using vacuum dye immersion challenge technique.

(b) Please provide the criteria for positive control and the results of positive control units tested.

Applicant's response: The results for dye immersion test were provided and summarized as follows:

Results of Dye Immersion test:

Test Article	Acceptance criteria	Batch 504-501-001	Batch 504-501-002	Batch 504-501-003
1	No evidence of dye in test article	0	0	0
2		0	0	0
3		0	0	0
4		0	0	0
5		0	0	0
6		0	0	0
7		0	0	0
8		0	0	0
9		0	0	0
10		0	0	0
11		0	0	0
12		0	0	0
13		0	0	0
14		0	0	0
15		0	0	0
Positive control	Evidence of dye in test article	+	+	+
Suitability		+	+	+
Negative control	No evidence of dye in test article	0	0	0
Negative control		0	0	0
Negative control		0	0	0

0 = No evidence of dye in the test article
+ = Evidence of dye in the test article

The results indicate that the test samples, positive control, and negative control met the acceptance criteria.

(c) The container closure integrity testing using visual assessment is acknowledged. However, the Agency prefers using an analytical method that is reproducible and more sensitive such as spectrophotometry. Therefore, please consider using a more sensitive method for container closure integrity testing.

Applicant's response: The applicant acknowledged that the spectrophotometric method is more sensitive than the visual method. However, it was indicated that the spectrophotometric method was not suitable for testing IBI-10090 drug product (b) (4)

(d) Please provide the limit of detection (LOD) or sensitivity of the analytical method used for detection of the dye and confirm that the test is sensitive enough to allow the detection of the entry and subsequent dilution of approximately 1-5 µL of the dye solution into a total volume of 1 mL of WFI.

Applicant's response: The validated LOD for water in the analytical method was determined to be (b) (4). The applicant states that the validated limit of detection (LOD) is determined visually by adding dye 1 µL at a time to the sample until the dye is visually detectable. As the sample itself may have some variability due to analyst variability and/or slight batch-to-batch variations during manufacture or raw materials, therefore, the reported LOD per test sample volume may also vary. The LOD for the 24-month registration stability batch was determined to be (b) (4) sample.

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

Adequate information has been provided regarding the CCIT.

Antimicrobial Effectiveness Testing- N/A

Reviewer's Assessment: N/A

The sterile drug product is manufactured as a single use vial. All the components of sterile administration syringe kit assembly are for single use. No AET is required.

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment: *Adequate*

Sufficient information is provided regarding the validation of the sterility test.

P.7 Container Closure

Summary table of the container closure system proposed

Reviewer's Assessment: Please refer to P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(P.8.2)
Proposed Expiry: 24 months

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

The stability data provided from the exhibit batches support the expiry dating of the drug product.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(3.2.P.8.2; Post-Approval Stability Protocol and Stability Commitment.pdf, p1/7)

Samples will be stored under long term conditions at 25 ºC/60 % RH in an inverted orientation. The product stability specification includes the following microbiological tests:

Marketed Stability Protocol for first three commercial batches (Storage conditions: 25 ºC/60 % RH; Vial orientation: Inverted)

Stability Test	Time (Months)								
	3	6	9	12	18	24	36	48*	60*
Bacterial Endotoxins	--	--	--	X	--	X	X	X	X
Sterility**	--	--	--	X	--	X	X	X	X
Container Closure Integrity Dye Immersion (Visual)	--	--	--	X	--	X	X	X	X

*Optional time points

** Only the first three marketed stability batches will be tested for sterility. Container closure Integrity test will replace sterility during annual testing of marketed batch as per "Guidance for industry: Container Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for sterile Products, Feb 2008"

Annual Marketed Stability Protocol (Storage conditions: 25 ºC/60 % RH; Vial orientation: Inverted)

Stability Test	Time (Months)								
	3	6	9	12	18	24	36	48*	60*
Bacterial Endotoxins	--	--	--	X	--	X	X	X	X
Container Closure Integrity Dye Immersion (Visual)	--	--	--	X	--	X	X	X	X

*Optional time points

Proposed expiry: A tentative shelf life of 24 months is proposed. The change or deterioration in the distributed drug product will be reported as required in 21 CFR§314.81(b) (1) (ii). The expiration dating period may be extended based on real-time data generated according to the registration and marketed stability protocols.

Post Approval Stability Commitment

(Module 3.2.P.8.2; Post-Approval Stability Protocol and Stability Commitment.pdf, p1/7)

Icon Bioscience commits to place the first three marketed batches of the subject drug product into their stability program. Thereafter, one batch of drug product manufactured each year will be placed annually on stability at long term conditions only as per the stability program.

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

The post approval protocol and stability commitment is in line with industry practice and acceptable.

P.8.3 Stability Data

Stability data generated for the registration batch of Dexamethasone suspension 9% (504-501-001) under accelerated conditions (40 ºC /75% RH; inverted), intermediate conditions (30 ºC/65% RH; inverted) and long term conditions (25 ºC /60% RH; inverted) until 24 month time point has been tested according to the stability schedule. The report was included in the submission. Bacterial endotoxins testing, sterility, and container closure integrity testing met the specifications at the initial (for long term, intermediate, and accelerated stability), 12 month time point (for intermediate and long term stability) and 24 month time point (for long term stability). The applicant stated that long term stability studies are ongoing.

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

The stability data provided for accelerated, intermediate and long term storage conditions for up to 24 months support the expiration dating of the drug product as proposed.

R Regional Information

Executed Batch Records

(3.2.R; Executed Batch Records.pdf)

Batch No.: 504-501-003
Batch Size: [redacted] (b) (4) vials [redacted] (b) (4) vials filled)

One representative executed batch record for registration stability batch number 504-501-003. The batch record consists of pre-sterilization batch record (500-501-003) and post-sterilization batch record (504-501-003), [redacted] (b) (4) .

The batch records indicated that [redacted] (b) (4) was used for [redacted] (b) (4)

The following information request was conveyed to the applicant on 10/10/2017 and the response was received on 10/17/2017.

IR:
Please confirm that validated process for [redacted] (b) (4) was used for the manufacturing of exhibit batch.

Applicant's response: The applicant confirmed that validated process for [redacted] was used for the manufacturing of exhibit batch 504-501-003.

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

The batch records confirm that validated [redacted] process was used for the manufacture of the exhibit batch.

Comparability Protocols: **N/A**

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

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

2.A. Package Insert

Storage temperature: [redacted] Route of administration: Intraocular injection; Container: Single administration dose

- **Post-dilution/constitution hold time- N/A**

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

No storage of the reconstituted drug product is proposed in the labeling. The applicant provided adequate instructions in the package insert to maintain product sterility.

Post-Approval Commitments:

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

List of Deficiencies:

NDA: 208912 APPLICANT: Icon Bioscience, Inc.

DRUG PRODUCT: Dexycu intraocular injection, 9 %

The Division of Microbiology Assessment has no comments at this time.

Primary Microbiology Reviewer Name and Date:
Hemlata Tamta, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA/BII
Date: 12/15/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
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Microbiologist
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