CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211911Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Approval

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

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on 1-29-2020.

Therefore, NDA 211911 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

DURYSTA™ (Bimatoprost (b) (4) implant), 10 μg is a biodegradable, sustained-release, preservative-free bimatoprost intracameral implant. The drug product is preloaded into a single-use applicator, (b) (4). The applicator is packaged with desiccant in a laminated aluminum foil pouch. The pouched applicator is placed in a (b) (4) tray with lid then packaged in a (b) (4) carton.

Proposed Indication(s) including Intended Patient Population	Reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).
Duration of Treatment	One implant in each eye
Maximum Daily Dose	As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The applicant cross-referenced the CMC information for the drug substance to DMF (b) (4) DMF (b) (4) was found adequate by Dr. Kabir Shahjahan on 1/22/2020.

Drug Product: Adequate

The drug product DURYSTA™ (Bimatoprost (b) (4) implant), 10 μg is a biodegradable, sustained-release, preservative-free bimatoprost intracameral implant. The drug product is preloaded into a single-use applicator, (b) (4). The applicator is packaged with desiccant in a laminated aluminum foil pouch. The pouched applicator is placed in a (b) (4) tray with lid then packaged in a (b) (4) carton. The drug product contains the following excipients: polymers poly (D,L-lactide), poly (D,L-lactide) acid end, poly (D,L-lactide-co-glycolide), and Polyethylene Glycol 3350. Polyethylene glycol 3350 is a compendial excipient. All the three grades of (b) (4) polymers are non-compendial and the CMC information for these polymers are cross-referenced to DMF (b) (4) and DMF (b) (4). Both DMFs are reviewed and found adequate. (b) (4) the assay at release is (b) (4) % of the labeled claim. As amended, the drug product specifications include tests for appearance, actuation force, content uniformity, drug release, identity, assay, impurities, sterility, and bacterial endotoxins. Drug substance is polymorph (b) (4) however, both polymorph (b) (4) and (b) (4) have the similar physical properties, therefore it is acceptable not to include polymorph testing in the specifications. Additionally, the drug substance is (b) (4), particle size distribution is considered as a low risk and is not part of the specifications. The applicant has provided the elemental impurity risk assessment and the elemental impurities present in the implant were below the control threshold. Therefore, the proposed specifications are acceptable. All analytical methods are described in reasonable detail and have been adequately validated. The proposed commercial applicator is the same applicator as that was used in the phase 3 studies, the clinical division advised that no CDRH consult is needed as the product is regulated as a drug NOT a drug-device combination product per 21 CFR 200.50. Based on its clinical use in ~100 patients, the applicator is considered acceptable for the commercial presentation.

The applicant provided long term stability data for two batches at the commercial strength 10 μg and two batches of 15 μg as follows: 36 moths/1 batch (10 μg) + 18 moths/1 batch (10 μg) and 36 moths/2 batches (15μg) + 24 moths/1 batch (15 µg) at long term storage of 5°C. The applicant also provided 24 months drug product stability data for three primary batches at both strength of 10 μg and 15 μg when stored at

the accelerated condition of 25 °C/60% RH. No significant trending noted for any of the quality attributes. The leachable study was performed for 3 registration batches for 24 months at 25 °C/60% RH and 1 batch for 36 months at 5 °C for both 10 μg and 15 μg strength, the leachable did not increase during stability suggesting no migration of volatile leachable from the container closure system. Based on the submitted stability data, the proposed shelf-life of 36 months for the drug product is granted when stored at 2°C - 8°C (36°F - 46° F).

Labeling: Adequate

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

Manufacturing: Adequate

The proposed drug product manufacturing process consists of (b) (4) . Information requests regarding (b) (4) content uniformity, (b) (4) implant weight, and (b) (4) etc were conveyed to the applicant and the response was found acceptable.
A pre-approval inspection was performed for the drug product manufacturer Allergan Pharmaceuticals, Ireland (FEI: 3002806285) on 10/21-10/25/2019, the final classification of the inspection is VAI after reviewing the response to 483 observations. All the other facilities are acceptable based on the profile. Therefore, the overall recommendation of "Approve" was entered for the NDA into Panorama by OPMA on 1/29/2020.

Biopharmaceutics: Adequate

The proposed drug release method and revised acceptance criteria are acceptable for batch release and stability testing. No bridging is needed as the formulation and manufacturing site of the proposed commercial product is identical to the formulation and manufacturing site of the drug product used in the clinical studies.

Microbiology (if applicable): Adequate

The applicant has provided adequate sterility assurance. The process is (b) (4). Both bacterial endotoxin and sterility testing are included in the drug product specifications.

C. Risk Assessment

From Initial Risk Identification	Assessment

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Sterility	Formulation Container closure • Process parameters Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Assay (API), stability	Formulation Container closure Raw materials	L		L	
Assay(preservative)	Formulation Container closure • Process parameters Scale/equipment	L		L	
Particulate matter	Formulation Container closure • Process parameters Scale/equipment	M		L	
Bacterial endotoxin	• Formulation • Container closure • Process parameters • Scale/equipment	M		L	
Drug release	• Formulation, variability in polymer (b) (4)) • parameter responsible for (b) (4) maintenance through the product shelf life •Scale-up/equipment	H		L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

NA

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

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

NA

Application Technical Lead Name and Date: Chunchun Zhang, Ph.D., 1/31/2020

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	211911
Assessment Cycle Number	0001, 0004
Drug Product Name/ Strength	DURYSTA™ (Bimatoprost [redacted] implant)/10 mcg
Route of Administration	Ophthalmic (intracameral) Insert
Applicant Name	Allergan, Inc.
Therapeutic Classification/ OND Division	Division of Ophthalmology Products
LD/RS Number	N/A
Proposed Indication	For the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Assessment Recommendation: **Adequate**

Assessment Summary: The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the drug release method and acceptance criteria, and **2)** bridging of the clinical and commercial drug products, and **3)** overall biopharmaceutics risk analysis.

1. DISSOLUTION TEST: Adequate

The approved drug release method and acceptance criteria are as follows:

Apparatus	Medium composition	Medium volume	Speed/ temp	Sample Time Points	Media volume replaced at each sampling time point	Drug release acceptance criteria
Thermo Scientific MaxQ Mini 4450 Shaker with 8 mL clear glass vial and open-top screw cap	2.4 mM Phosphate Buffered Saline (PBS), pH 7.6	2 mL	Static/ 37°± 1°C,	Day 1 (24 hours), Day 4, Day 7, Day 10, Day 14, Day 21, and Day 28	1.5 mL of fresh media is added yielding a total volume of 2.0 mL after replenishment	Day 1: NMT [redacted]% Day 14: [redacted]% Day 28: NLT [redacted]% released Note: L2 and L3 stage is also proposed.

The proposed drug release method and revised acceptance criteria are **acceptable** for batch release and stability testing.

2. BRIDGING: Adequate

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

3. RISK ASSESSMENT: Adequate

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

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # 0004	Comments
Drug release	High	Bimatoprost SR implant was designed with three polymers: PLA+PLGA+PEG. (b) (4) the expected extent of release is up to three months.	Medium	The drug release method has discriminatory capability with respect to formulation and process variability. Due to the complexity of the drug product design, in vitro drug release testing alone may not be adequate to support future CMC change.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 **0004** **0009**	**05/06/2019** **07/10/2019** **10/18/2019**

Highlight Key Issues from Last Cycle and Their Resolution: None.

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

B.1 BCS DESIGNATION

BCS designation is not applicable since this is not an oral dosage form.

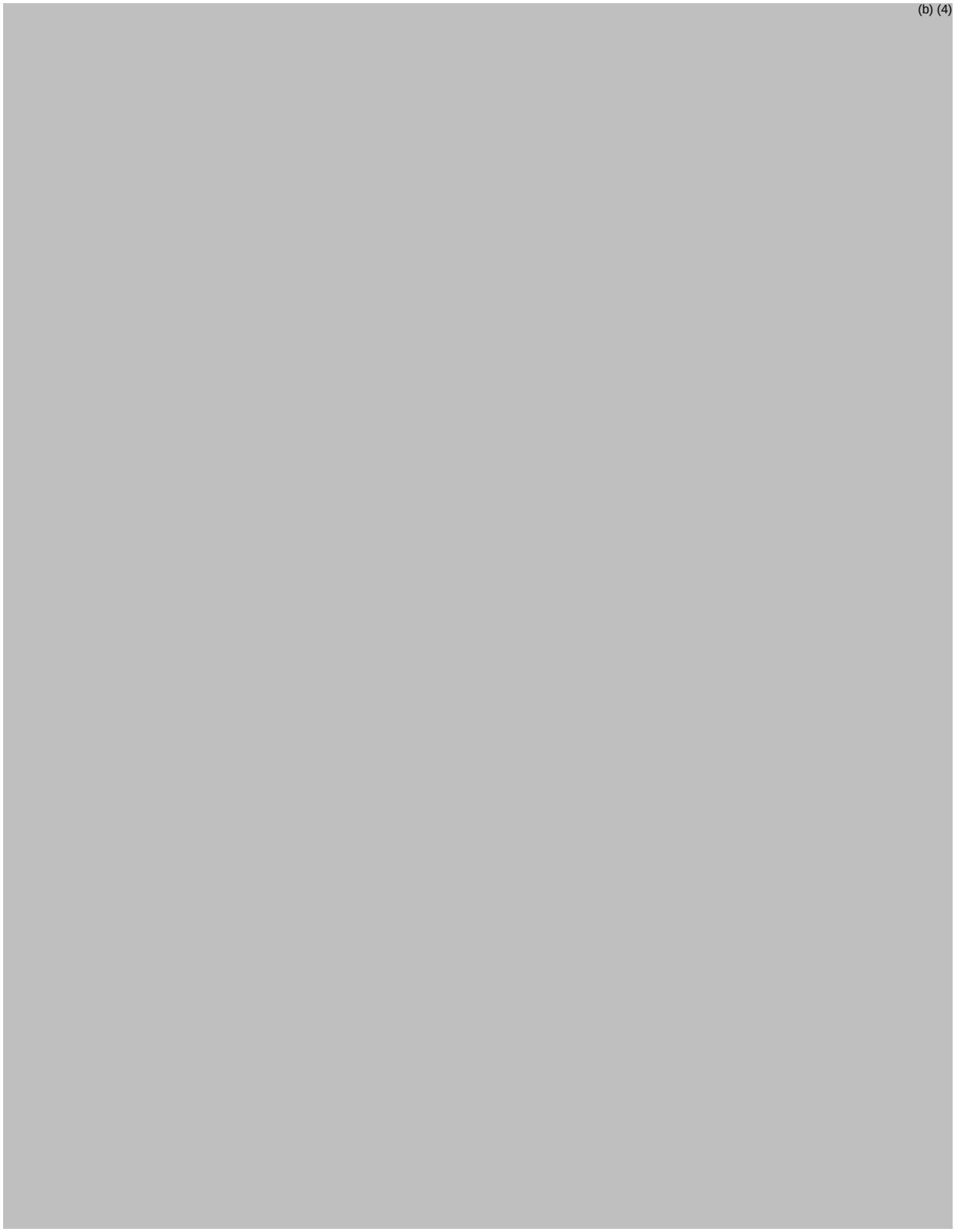
Assessment: N/A

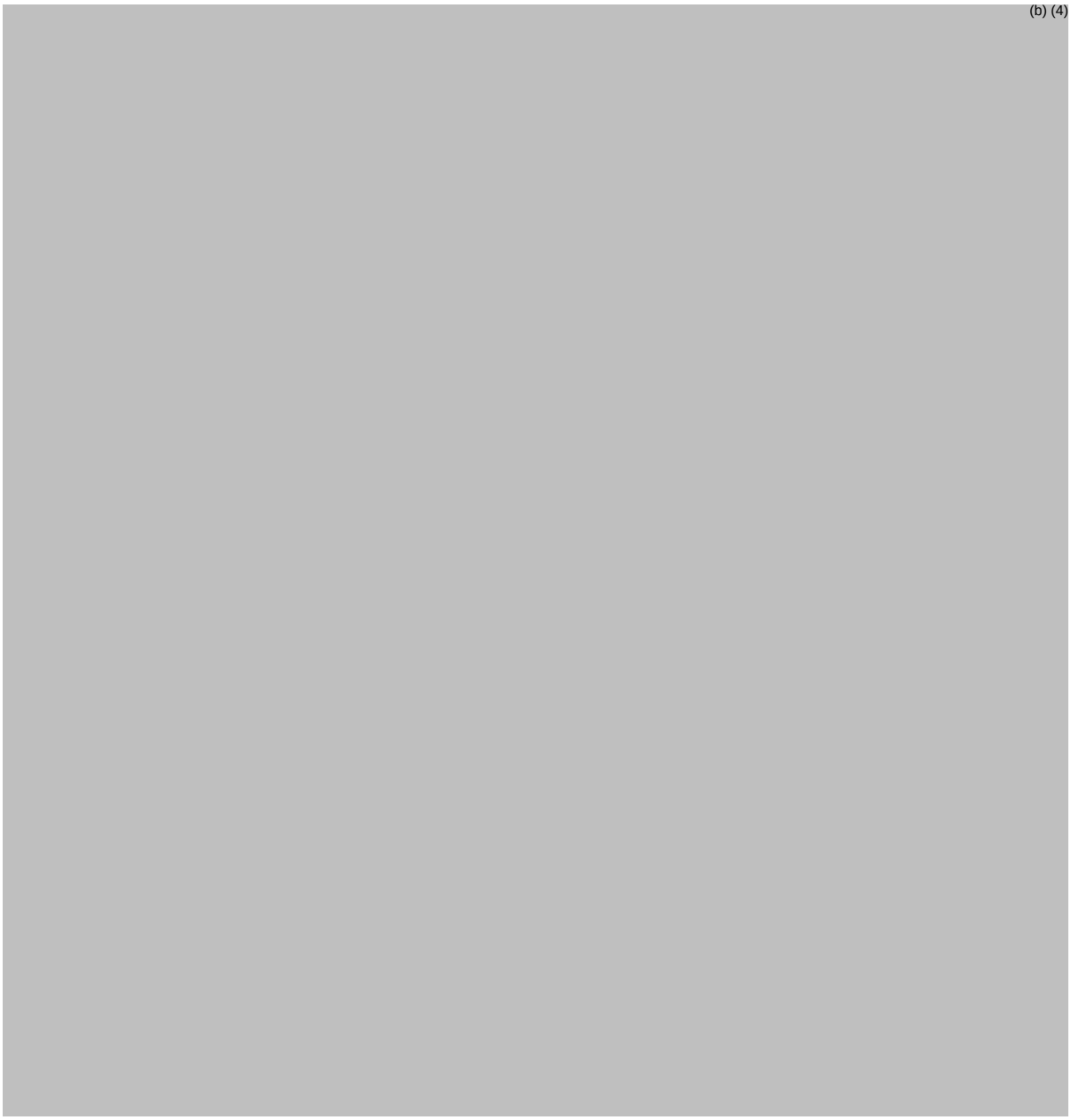
B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

The drug product is an extended release ophthalmic implant (drug delivery system (DDS)) that contains three polymers: PLA+PLGA+PEG. (b) (4) the expected extent of drug release is up to three/four months. (b) (4) The Bimatoprost Implant is approximately 0.2 mm in diameter and approximately 1.1 mm and (b) (4) mm in length for the 10 µg and 15 µg doses, respectively. The drug release mechanisms for this PLGA based drug delivery system (DDS) are associated with (b) (4) polymer degradation/erosion. (b) (4) . The proposed drug product will result in sustained drug levels in the target tissue (eye), and result in very low systemic concentrations. Because of the dosage form design resulting in an extended drug release profile, an accelerated drug release method for quality control purpose is required. Upon request by the FDA (dated June 26, 2019), a complete in vitro drug release method development report, PD-TRPT-00822[1], was provided under amendment (document # 0004) dated 7/10/2019. During the early stage formulation development (Phase 1 and 2), the following drug release method was evaluated:

(b) (4)

[1] \\cdsesub1\evsprod\NDA211911\0004\m3\32-body-data\32p-drug-prod\bimatoprost-sr-implant\32p2-pharm-dev





Drug release method's discriminatory capability: The proposed drug release method (regulatory/phase 3 method) demonstrates adequate discriminating capability with respect to variations in the drug product formulation (polymer types and levels) and critical manufacturing parameters, (b) (4) , and quality changes of stability samples as follows:

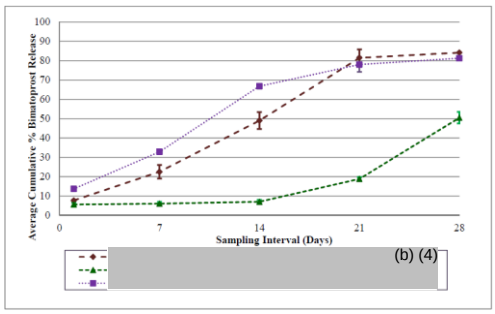


Fig 2. Impact of different (b) (4) (b) (4) (b) (4) on drug release (proposed QC method).

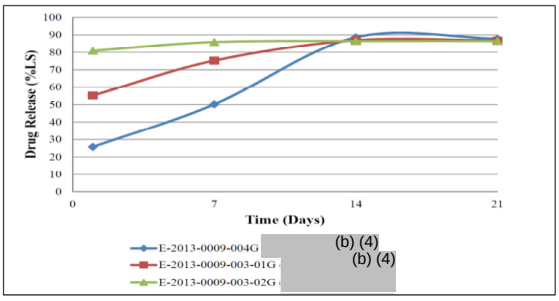


Fig.3. Impact of manufacturing process ((b) (4) (b) (4)) on drug release (proposed QC method).

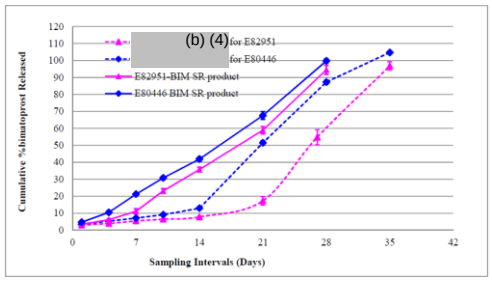


Fig. 4. Impact of (b) (4) (b) (4) (b) (4)) on drug release (proposed QC method).

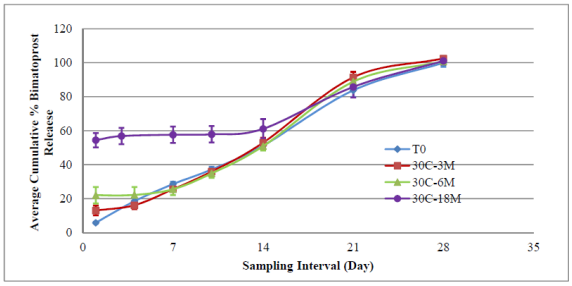


Fig. 5. Drug release under accelerated storage conditions (storage condition: 2-8°C)

Initially proposed drug release acceptance criteria:

Table 5. Initially proposed drug release acceptance criteria

Test	Acceptance Criteria
Drug Release (% LS) Level L1 (n =12)	Day 1: NMT (b) (4)% Day 14: (b) (4)% - (b) (4)% released Day 28: NLT (b) (4)% released
Level L2 (n = 12)	The average value of the 24 units (L1+L2) lies within the L1 ranges. No individual value (n = 24) lies outside the following ranges: Day1: NMT (b) (4)% released Day 14: (b) (4)% - (b) (4)% released Day 28: NLT (b) (4)% released
Level L3 (n =24)	The average value of the 48 units (L1+L2+L3) lies within the L1 ranges. Not more than 2 of the 48 units are outside the following ranges: Day 1: NMT (b) (4)% released Day 14: (b) (4)% - (b) (4)% released Day 28: NLT (b) (4)% released No individual value (n = 48) is outside the following ranges: Day1: NMT (b) (4)% released Day 14: (b) (4)% - (b) (4)% released Day 28: NLT (b) (4)% released

Data submitted to support the initially proposed drug release specification: A total of 22 batches (14 Phase III clinical study batches and 8 primary stability batches) were manufactured and tested with the phase 3/regulatory drug release method. Batch release data are summarized in the following table:

Table 6. Drug release data of phase 3 and registration batches of the proposed Bimatoprost Implant (highlighted box represent lowest and highest amount of drug release)

Phase	Lot	Dosage	Average Cumulative % LS of Bimatoprost Released						
			Day 1	Day 4	Day 7	Day 10	Day 14	Day 21	Day 28
Phase 3	13861A1A	10 µg	6	21	33	41	52	74	98
	13908A1A	10 µg	6	15	25	35	47	75	97
	14084A1A	10 µg	11	21	30	39	51	82	101
	14121A1A	10 µg	11	19	28	37	50	82	101
	14123A1A	10 µg	5	11	25	35	49	81	99
	E83014	10 µg	4	7	12	26	39	66	98
	13875A1A	15 µg	5	17	27	35	46	72	102
	13909A1A	15 µg	4	14	25	35	48	81	102
	E75845	15 µg	6	15	26	34	45	76	101
	14083A1A	15 µg	8	14	26	35	47	78	102
	14122A1A	15 µg	4	11	24	33	47	79	99
	E80446	15 µg	5	10	21	31	42	68	100
	E82951	15 µg	3	6	11	23	36	59	95
	E83298	15 µg	4	8	15	27	39	63	98
Registration	E73673-11047X	10 µg	6	19	29	37	51	84	100
	E73747-11047X	10 µg	11	19	30	39	53	86	101
	E74873-11047X	10 µg	6	12	25	35	48	78	101
	E78123-11047X	10 µg	17	24	32	40	54	92	96
	E73673-11048X	15 µg	6	18	27	35	48	80	98
	E73747-11048X	15 µg	8	17	27	35	46	76	99
	E74873-11048X	15 µg	6	16	27	35	47	74	100
	E76934-11048X	15 µg	10	23	31	40	53	86	106
Mean (%LS) Phase 3 and Registration			7	15	25	35	47	77	100
Standard Deviation			3	5	6	5	5	8	2
Specification Limits (% LS)			(b) (4)						

(b) (4)

Fig.6. Individual implant cumulative drug release profile

On September 16, 2019, the applicant was asked to provide the following information:

IR Comment: *Provide individual drug release data of all phase 3 clinical and registration batches at the 14-day time point. Clearly indicate the age of the batch at the time of drug release testing.*

The Applicant responded on 09/23/2019[2] and provided the following table:

Table. 7. Summary Results for Day-14 Drug Release of Phase 3 and Registration Batches

Batch No.	Purpose	Dosage Strength	Manufacturing Date	Testing Date	Batch Age at the Time of Testing (Days)	Acceptance Criteria for Drug Release at Day-14 (% LS)	Individual Drug Release (% LS)	Average Drug Release (% LS)
13861A1A	Phase 3	10 µg	04 Jun 2014	27 Aug 2014	84	Level L1 (n=12): (b) (4)% released Level L2 (n=12): The average value of the 24 units (L1 + L2) lies within the L1 ranges. No individual value (n=24) lies outside the range of (b) (4)% released. Level L3 (n=24): The average value of the 48 units (L1 + L2 + L3) lies within the L1 ranges. Not more than 2 of the 48 units are outside the range of (b) (4) (b) (4) released. No individual value (n=48) lies outside the range of (b) (4) released.	(b) (4)	52
13908A1A	Phase 3	10 µg	04 Jun 2014	01 Dec 2014	180			48
14084A1A	Phase 3	10 µg	21 Mar 2016	20 Jun 2016	91			51
14121A1A	Phase 3	10 µg	21 Mar 2016	18 Oct 2016	211			50
14123A1A	Phase 3	10 µg	14 Sep 2016	03 Jan 2017	111			49
E83014	Phase 3	10 µg	23 Jan 2018	27 Apr 2018	94			39
E84330	Phase 3	10 µg	23Aug 2018	26 Nov 2018	95			41
E84932	Phase 3	10 µg	23Aug 2018	11 Mar 2019	200			46
13875A1A	Phase 3	15 µg	04 Jun 2014	27 Aug 2014	84	Level L1 (n=12): (b) (4)% released Level L2 (n=12): The average value of the 24 units (L1 + L2) lies within the L1 ranges. No individual value (n=24) lies outside the range of (b) (4)% released. Level L3 (n=24): The average value of the 48 units (L1 + L2 + L3) lies within the L1 ranges. Not more than 2 of the 48 units are outside the range of (b) (4)% released. No individual value (n=48) lies outside the range of (b) (4)% released.	(b) (4)	46
13909A1A	Phase 3	15 µg	04 Jun 2014	01 Dec 2014	180			49
E75845-11048XRD	Phase 3	15 µg	21 Apr 2015	27 Jul 2015	97			45
14083A1A	Phase 3	15 µg	21 Mar 2016	20 Jun 2016	91			48
14122A1A	Phase 3	15 µg	14 Sep 2016	03 Jan 2017	111			47
E80446	Phase 3	15 µg	20 Feb 2017	15May2017	84			42
E82951	Phase 3	15 µg	23 Jan 2018	26 Mar 2018	62			36
E83298	Phase 3	15 µg	23 Jan 2018	18 Jun 2018	146			39
E84118	Phase 3	15 µg	23Aug 2018	29 Oct 2018	67			39
E84500	Phase 3	15 µg	23Aug 2018	11 Mar 2019	200			40

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E73673_10	Registration	10 µg	11 Jun 2014	16 Mar 2015	278	Level L1 (n=12): (b) (4)% released Level L2 (n=12): The average value of the 24 units (L1 + L2) lies within the L1 ranges. No individual value (n=24) lies outside the range of (b) (4)% released. Level L3 (n=24): The average value of the 48 units (L1 + L2 + L3) lies within the L1 ranges. Not more than 2 of the 48 units are outside the range of (b) (4)% released. No individual value (n=48) lies outside the range of (b) (4)% released.	(b) (4)	51
E73747_10	Registration	10 µg	24 Jun 2014	06 Apr 2015	286			53
E74873_10	Registration	10 µg	26 Nov 2014	20 Apr 2015	145			48
E73673_15	Registration	15 µg	11 Jun 2014	12 Jan 2015	215			48
E73747_15	Registration	15 µg	24 Jun 2014	12 Jan 2015	202			46
E74873_15	Registration	15 µg	26 Nov 2014	17 Feb 2015	83			47
E76934_15	Registration	15 µg	21 Apr 2015	02 May 2016	377			53
E78123	Registration	10 µg	21 Mar 2016	19 Jun 2017	455			54

From the provided table above (Table 7*),* the lowest individual phase III batch drug release at 14-day time point observed, was (b) (4)% (Batch # E82951, phase III) and the highest drug release was (b) (4)% (Batch 13908A1A, phase III). Note that the highest drug release ((b) (4) was observed only from two individual units. Most of the drug release data are between 34%-55%. On the other hand, the registration batches (see table 7) shows comparatively a consistent drug release at the 14-day time point. Therefore, the drug release acceptance range was recommended to be tightened as follows:

14 day: (b) (4)%

IR Comment sent on October 4th, 2019: Based on the provided data on all clinical and registration batches, the FDA recommends that you tighten the drug release acceptance criterion range at the 14-day time point as follows: (b) (4)% (L1). Revise your drug product specification including appropriate revised L1, L2, and L3 criteria per USP for batch release and stability testing accordingly.

Applicant's Response on October 18th, 2019: *Allergan agrees to tighten the Level 1 lower specification limit from (b) (4) to (b) (4)% LS and recommends revising the upper specification limit from (b) (4) to (b) (4)% LS based on the evaluation of the Phase 3 batch release and registration stability data. The following provides the justification for the upper limit of (b) (4)% at the 14-day time point. The statistical data analysis summary of day 14 drug release data from Phase 3 and registration batches is shown below: The 3-sigma (95% confidence) data analysis approach was performed and the (mean ± 3 sigma) values and the standard deviation were obtained. The mean ± 3 sigma values and the standard deviation from all the Phase 3 and registration batch release data are 31% LS (lower value) and 62% LS (upper value) with a standard deviation of 5% LS. The range of day 14 drug release is from (b) (4)% to (b) (4)% LS at release (T_{zero}). The mean ± 3 sigma values and the standard deviation from the registration stability data are 39% LS (lower value) and 63% LS (higher value) with a standard deviation of 4% LS. The range of day 14 drug release in stability is from (b) (4)% to (b) (4)%. With reference to the 3-*

sigma values and the variabilities observed, the proposed upper limit for day 14 drug release at (b) (4) % will frequently trigger the analysis of level 2 and/or level 3 testing. Based on all the data, day 14 drug release data available to date and with the consideration that the variability observed is inherent to the accelerated drug release method and is not caused by changes in implant quality, Allergan proposes that the L1 specification limits for release and shelf-life for day 14 drug release be tightened to (b) (4) % LS, as follows:

Test	Acceptance Criteria	Method
Drug Release (% LS) Level L1 (n =12)	Day 1: NMT (b) (4) % Day 14: (b) (4) % released Day 28: NLT (b) (4) % released	HPLC/UV
Level L2 (n = 12)	The average value of the 24 units (L1+L2) lies within the L1 ranges. No individual value (n = 24) lies outside the following ranges: Day1: NMT (b) (4) % released Day 14: (b) (4) % released Day 28: NLT (b) (4) % released	
Level L3 (n =24)	The average value of the 48 units (L1+L2+L3) lies within the L1 ranges. Not more than 2 of the 48 units are outside the following ranges: Day 1: NMT (b) (4) % released Day 14: (b) (4) % released Day 28: NLT (b) (4) % released No individual value (n = 48) is outside the following ranges: Day1: NMT (b) (4) % released Day 14: (b) (4) % released Day 28: NLT (b) (4) % released	

Assessment: A*dequate*

The proposed phase 3/regulatory accelerated drug release method (capturing the three/four months of in vivo release) is to evaluate the batch-to batch consistency and stability behavior with no intent of matching the in vivo behavior. The drug release method was evaluated for robustness through DOE studies and was found to be acceptable. The method showed enough discriminatory capability with respect to formulation change and critical manufacturing process variability. One material attributes that was not tested for its impact on drug release includes API's solid-state form. However, the risk is mitigated through stability studies using modulated differential scanning calorimetry (mDSC) and x-ray powder diffraction (XRPD) methods, demonstrating that Bimatoprost remained as Polymorph (b) (4) in the drug product matrix with no conversion of Polymorph (b) (4) to Polymorph (b) (4) when stored at long

term storage condition at 5°C and at accelerated condition at 25°C/60%RH for up to 3 years. Based on the overall submitted information, the proposed phase 3/regulatory drug release method is found acceptable.
The proposed drug release acceptance criteria for Day 1 (NMT (b) (4)%) and for Day 28 (NLT (b) (4)%) are found acceptable. The proposed drug release acceptance range for Day 14 ((b) (4)%) was found too wide. In addition, the proposed L1, L2 and L3 levels do not follow USP 724 with regards to sample numbers and levels. Even though the revised proposed L1 ((b) (4)% for Day 14) is not as tight as the originally recommended L1 ((b) (4)% for Day 14), the proposed L3 is actually tighter than the L3 originally recommended per USP 724. For example, the revised proposed L3 level for Day 14 (no unit outside (b) (4)%) is tighter than the recommended L3 was in the information request described above (no unit outside (b) (4)% - based on L1 (b) (4)%). Based on the additional data and the proposed L1, L2, and L3 levels, the Applicant's revised drug release acceptance range at the 14-day time point ((b) (4)% for Level 1), and the proposed L2, L3 per above Table, are acceptable for quality control of the proposed drug product

B.12 BRIDGING OF FORMULATIONS
The formulation and manufacturing site of the proposed commercial product is identical to the formulation and manufacturing site of the drug product used in the clinical studies. Therefore, bridging is not needed.

Assessment: ***Adequate***

B. 13 BIOWAIVER REQUEST *None.*

R. REGIONAL INFORMATION

Comparability Protocols: None

Post-Approval Commitments: None

Lifecycle Management Considerations
Any future change with respect to manufacturing site change and process change need to be bridged appropriate for this product. In vitro drug release testing alone may not be sufficient to support such bridging.

BIOPHARMACEUTICS LIST OF DEFICIENCIES
None

Primary Biopharmaceutics Assessor's Name and Date: Akm Khairuzzaman, Ph.D. 12/02/2019

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MICROBIOLOGY

IQA Review Guide Reference

NDA: 211911

Drug Product Name / Strength: Durysta (bimatoprost (b) (4) implant), 10 mcg

Route of Administration: Intracameral Implant

Applicant Name: Allergan, Inc.

Manufacturing Site: Allergan Pharmaceuticals, Ireland, Castlebar Road, Westport, County Mayo, Ireland

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

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

Justification (ANDA only): N/A

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

List Submissions Being Reviewed: 05/06/2019; 06/21/2019 and 09/23/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: A Microbiology Information Request was issued to the applicant on 14 June 2019, and the applicant forwarded responses on 21 June 2019. A second IR was sent to the applicant on 9/9/2019 and a response was received on 9/23/2019.

Concise Description Outstanding Issues Remaining: None

Supporting Documents: N/A

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

S Drug Substance – The drug substance is non-sterile.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Bimatoprost SR 10 µg is an intracameral implant designed for the reduction of intraocular pressure and consist of bimatoprost in a solid polymer sustained-release drug delivery system. The rod-shaped implant is preloaded into a single-use applicator, (b) (4), to facilitate injection of the implant directly into the anterior chamber of the eye.

- **Composition of Bimatoprost SR Implant**

Component	Function	Quality Standard	Concentration	
			% w/w	µg/Dose
Bimatoprost	Drug substance	In-house[a]	(b) (4)	10
(b) (4) Poly (D,L-lactide)	(b) (4)	In-house		(b) (4)
(b) (4) Poly (D,L-lactide-co-glycolide)		In-house		
(b) (4) Poly (D,L-lactide) Acid End		In-house		
Polyethylene Glycol 3350		USP		
		Total	100	

- (b) (4) **Applicator**
  The Bimatoprost SR implant is preloaded within (b) (4) the single-use applicator. The applicator is designed specifically to deliver the rod-shaped implant directly into the anterior chamber of the eye. The applicator contains a 28-gauge ultra-thin wall hypodermic needle lubricated with silicone. (b) (4) . The applicator and its individual components are described in the table below:

Component	Supplier	Sub-Component	Function	Raw Material	Biocontact
Housing cap	(b) (4)	Housing Cap		(b) (4)	None
Needle subassembly		Needle			Transient
		Needle Hub			None
Back half subassembly		Safety Cap			None
		Plunger			Transient
		Button			None
		Safety Tab			None
		(b) (4)			None
		Left Housing			None
		Right Housing			None
		Nameplate			None
(b) (4)					Direct

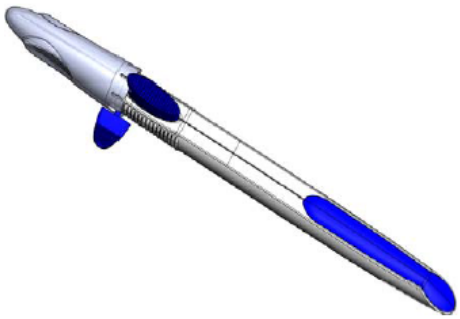
- **Description of container closure system –**

  The finished product, (b) (4) applicator containing the implant (Figure 1), is packaged in a laminated aluminum foil pouch with a 3-gram desiccant sachet. The three components that contacts the implant are: plunger, needle, and (b) (4). The foil pouch serves as the primary container closure for the drug product and provides the moisture and microbial barriers. The primary packaging components are provided in the table below:

Table 1 Primary Packaging Components

Component Description	Manufacturer	Materials of Construction
Laminated foil pouch		(b) (4)
Desiccant packet (b) (4)		

Figure 1 (b) (4) **Applicator**



(b) (4)

Figure 2 Section View of Needle

(b) (4)

Number	Component
1	Safety Cap
2	Housing Cap
3	Needle
4	Needle Hub
5	Plunger
6	Button
7	Safety Tab
8	(b) (4)
9	Left Housing
10	Right Housing
11	Nameplate
12	(b) (4)

The applicator is then packaged with desiccant into a laminated foil pouch.

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

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

The following Information Request was issued to the applicant on June 14, 2019:

Provide a description of the drug product container-closure integrity test method, a description of controls, and a summary of results.

Applicant Response:

(Section 1.11.1 quality information amendment: 1.pdf, dated 6/21/2019 and 3.2.P.7 container closure system.pdf)

The container/closure system used for validation was:

Test	Step/Component	Method	Acceptance Criteria
(b) (4)			
Seal Integrity Creep	sealed pouched final product release and stability	DP-PT163	(b) (4) psi for (b) (4) sec.

The applicant states that the laminated foil pouch maintains a sterile barrier for the (b) (4) applicator containing the implant. Additionally, the needle housing cap covers the sterile needle, and the safety cap in turn covers the housing cap. Therefore, the foil pouch serves as a third barrier between the sterile needle/implant and the external environment.

Seal integrity creep testing will be performed on laminated foil pouch at the release and stability (and also before (b) (4)) while (b) (4). Additionally, seal inspection (visual) will be performed.

(b) (4)

Note to Reviewer: The applicant has not provided the details of the test and information is requested below.

Test method: Seal integrity creep test
The test is performed to test the integrity of the applicator foil pouch seal. The instrument used is: Carleton Technologies Test-A-Pack Seal Strength Tester Series 2000

Test report# (b) (4) ASET-DP-PT163.00

The test was performed by cutting the applicator pouch in half (lengthwise) and securing it on the test apparatus following pressurization with air to (b) (4) psi pressure. The pouch pressure is then monitored for loss of pressure for (b) (4) seconds. Also, the foil pouch is observed for leaks.
Acceptance criteria:
The pouch seal is considered integral and the test is passed if the
(b) (4) psi pressure is maintained for (b) (4) seconds and no leaks are observed for either of the pouch halves

The number of samples tested is not provided. The applicant states that typically 10 intact pouches are carefully cut in half and test the 20
individual pouch-halves.
The applicant states that no validation is required for the Seal integrity creep test Method ASET-DP-PT163.00 and the accuracy of the method is verified by meeting the System Suitability criteria for the instrument.
Primary batches Batch E73673_10, Batch E73747_10, Batch E74873_10 and E78123 meets the test requirement.

The following Information Request was issued to the applicant 09 September 2019

Regarding the primary container closure system integrity test (CCIT):

a) *It is acknowledged that the* (b) (4) *test. However, the information provided to validate said test is insufficient for review. Please provide a detailed description of the test procedure* (b) (4) *, and the test results.*

b) *Confirm that the test units were exposed to at least the production* (b) (4) *conditions prior to* (b) (4) *. Alternatively, provide additional successful* (b) (4) *results using test units exposed to at least the minimum production* (b) (4) *conditions.*

Applicant Response: (a and b)

An individual pouched unit is placed into an individual (b) (4) resulting in a

(b) (4)

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

Sufficient information has been provided to demonstrate the drug product container closure integrity.

Antimicrobial Effectiveness Testing

N/A. The subject drug product is a single-use; antimicrobial effectiveness testing is not required.

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

P.3 Manufacture

P.3.1 Manufacturers

Drug product manufacturing:

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(b) (4)

P.8 Stability

P. 8.1 Stability Summary and Conclusion

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

Proposed Expiry: 36 months when stored refrigerated (2°C – 8°C).

Stability testing includes testing under accelerated (25 °C/60% RH) and long-term (5ºC) conditions. Accelerated conditions are tested at 0, 12, 24 and 36 months and the long-term conditions are tested at 0, 12, 24 and 36 months. Sterility and bacterial endotoxins test for both implant and needle met the proposed acceptance criteria of NMT (b) (4) and NMT (b) (4) for BET for implant and needle respectively and sterility test met the criteria "meets compendial requirements"
Four registration batches (2 batches for each dose) and one phase 3 batch were set up on stability at 5°C.

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 (Implant)	USP <71>	Sterile
Sterility (Needle)		Sterile
Bacterial Endotoxins Test (Implant)(EU/implant)	USP <85>	NMT (b) (4)

Bacterial Endotoxins Test (Needle) (EU/needle)		NMT (b) (4)

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

Stability storage conditions: 5±3°C

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
Sterility	X				X			X	X
endotoxin	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

Please see P.8.1 and P.8.2

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 #: E78123

The batch records did confirm that the proposed (b) (4) process was used for the manufacture of the exhibit batch.
Note to Reviewer: The applicant has provided sterility documents (b) (4) in 3.2.R. The sterility and endotoxin results on the exhibit batch record met the specification at 0 month and 12 months' time point.

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: Store refrigerated at 2°C to 8°C (36°F to 46°F).
Route of administration Intracameral Implant, Single use

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***

APPEARS THIS WAY ON ORIGINAL

List of Deficiencies: None

APPEARS THIS WAY ON ORIGINAL

Primary Microbiology Reviewer Name and Date:
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Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Neal Sweeney, Ph.D. (12/01/2019)
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