CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209529Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 209529

Assessment #2

Drug Product Name	VESIcare LS (solifenacin succinate) oral suspension
Dosage Form	Oral suspension
Strength	5 mg/5 mL (1 mg solifenacin succinate per mL, equivalent to 0.75 mg solifenacin per mL)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Astellas Pharma US, Inc.
US agent, if applicable	-
Application Type	505(b)(1)
NDA Classification Code*	Type 3, New dosage form
Combination Product	na

* Previously referred to as the "Chemistry Classification Code."

Submission(s) Assessed	Document Date	Discipline(s) Affected
Class 2 Resubmission after Complete Response (0031)	11/27/2019	All
Quality/Response to IR (0033)	01/14/2020	Product Quality Microbiology
Quality/Response to IR (0034)	02/12/2020	Product
Quality/Response to IR (0035)	02/20/2020	Manufacturing
Quality/Response to IR (0036)	03/05/2020	Manufacturing
Labeling/Labels (0038)	03/23/2020	ONDP Labeling
Labeling/Labels (0039)	04/06/2020	ONDP Labeling
Quality/Response to IR (0040)	04/16/2020	Product, Manufacturing
Labeling/PI (0041)	05/07/2020	ONDP Labeling
Labeling/PI (0042)	05/13/2020	ONDP Labeling
Labeling/Labels, PPI (0043)	05/15/2020	ONDP Labeling
Labeling/PI, PPI (0044)	05/19/2020	ONDP Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sukhamaya (Sam) Bain	Donna Christner
Drug Product / Labeling	Zhengfang Ge	Moo-Jhong Rhee
Manufacturing	James Norman	Jean Tang
Microbiology	Andrew Brown	Nandini Bhattacharya
Biopharmaceutics	Assadollah Noory	Vidula Kolhatkar
RBPM	Marquita Burnett	
ATL	Mark Seggel	
Laboratory (OTR)	-	-
Environmental	Zhengfang Ge James Laurenson	-

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Astellas Pharma's resubmission of 505(b)(1) New Drug Application 209529, for VESIcare LS (solifenacin succinate) oral suspension, 1 mg/mL, is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, and bioavailability of the drug product. The previously identified product quality microbiology issues have been adequately resolved. To ensure that the requisite product viscosity is maintained throughout the shelf life and in-use period, the acceptance tests for (b) (4) have been revised (b) (4) (b) (4).

The drug product labels (container / carton) as submitted on May 15, 2020, and the labeling (prescribing information, PPI) as submitted on May 19, 2020, is accurate, complete and complies with the requirements under 21 CFR 201.

The drug substance manufacturing, packaging and testing facility has acceptable CGMP status. The (b) (4) drug product manufacturing site, which was cited as deficient in the August 28, 2017 Complete Response Letter, was recently found acceptable via the Sec. 704 (a)(4) (FDASIA Sec. 706) Records Request process. The associated product packaging and testing facilities also have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on May 8, 2020.

An expiration dating period of 24 months for product packaged in amber PET bottles and stored at 20°C to 25°C is granted.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Product Description:
VESIcare LS is an oral suspension containing 1 mg/mL of solifenacin succinate, equivalent to 0.75 mg/mL solifenacin. Inactive ingredients in

the aqueous suspension include Polacrilin Potassium, NF, (b) (4) (b) (4) (b) (4). Other components include Carbomer Homopolymer NF (Type B), (b) (4) (b) (4) methylparaben and propylparaben, (b) (4) natural orange flavor, propylene glycol, and (b) (4) (b) (4) sodium hydroxide. (b) (4)

The drug product is filled to a volume of 150 mL in amber polyethylene terephthalate (PET) bottles with polyethylene / polypropylene child-resistant caps. The daily dose is weight-based and ranges from 2 mL to 10 mL. The dose is administered using an oral syringe supplied by the dispensing pharmacy.

Background:
Solifenacin succinate is a water-soluble muscarinic antagonist that was first approved on November 19, 2004 under NDA 21518. VESIcare (solifenacin succinate) tablets, 5 mg and 10 mg, are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

The oral suspension formulation was developed to facilitate treatment of pediatric patients. NDA 209529 was submitted February 28, 2017 and was granted a Priority review because of the potentially significant utility in the treatment of pediatric patients with overactive bladder resulting from a neurologic lesion. In this population, the most common cause of NDO is a congenital neural tube defect.

Proposed Indication(s) including Intended Patient Population	Solifenacin succinate oral suspension, 1 mg/mL, is indicated for the treatment of pediatric patients aged 2 years and older with neurogenic detrusor overactivity (NDO).
Duration of Treatment	Indefinite.
Maximum Daily Dose	Up to 10 mg solifenacin succinate per day.
Alternative Methods of Administration	Not applicable.

B. Quality Assessment Overview

Note: As discussed in the August 21, 2017 OPQ Quality Assessment #1, NDA 209529 submitted February 28, 2017, was found "Not Ready for Approval in its present form per 21 CFR 314.125(b)(1) and 314.125(b)(13)."

Three approvability issues were described in the August 28, 2017 Complete Response Letter:

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

2. The quality of (b) (4) as currently supplied by (b) (4) is not adequately controlled, resulting in drug product batches that do not meet the proposed drug product specification.

3. The drug product specification and post-approval stability program do not include the test methods and acceptance criteria to demonstrate that the product is free, and remains free, of the objectionable microorganisms (b) (4) (b) (4).

The current status of NDA 209529 as well as the OPQ assessment of Astellas' November 27, 2019 responses to the Complete Response Letter are summarized below.

Drug Substance: Adequate

Drug substance CMC is provided by cross-reference to Astellas Pharma's NDA 21518. The drug substance CMC is adequate based upon the continued approved status of NDA 21518. The current information on the drug substance supports **approval** of NDA 209529. See Chapter I, Drug Substance, of this IQA for additional comments.

Drug Product: Adequate

(b) (4) as supplied by (b) (4) is included in the formulation (b) (4). As discussed in detail in the August 21, 2017 OPQ Quality Assessment, in early June 2017 (and prior to the scheduled PAI of (b) (4)) Astellas reported that an out-of-specification (OOS) investigation of finished product viscosity test failures had been initiated.

Because the issue was not resolved by the time of the PAI, a facility 'withhold' recommendation was made (see the 'Manufacturing' discussion

below). A root cause analysis linked the OOS results to previously implemented changes to (b) (4) manufacture of (b) (4) (b) (4) (b) (4) added to the drug product formulation. (b) (4) could no longer guarantee that the (b) (4) supplied to Astellas, although still meeting compendial requirements, would be comparable to that used in the manufacture of the phase 3 investigational material. Astellas was therefore advised to evaluate other potential tests that could identify suitable batches of (b) (4).

After further research and development, Astellas determined that (b) (4) the content of (b) (4) in the formulation (b) (4) resulted in finished product meeting the previously established viscosity requirements. No changes in the raw material specification were reported.

During the recent "paper' inspection (see the 'Manufacturing' discussion below) of the commercial drug product manufacturing site (b) (4) (b) (4), the Agency became aware of additional (b) (4) testing performed on (b) (4) that had not been reported in the resubmission. The NDA was subsequently updated (0040) to include an additional (b) (4) test for viscosity (b) (4) (b) (4) solution. Note that the USP monograph test specifies testing of a 0.5% solution. Results from testing (b) (4) better correlate with finished product viscosity.

The applicant has demonstrated that drug product with the requisite quality can be manufactured consistently. Stability data from formulation B and the final commercial formulation show comparable trends; data from formulation B can therefore be used to support the expiration dating period (24 months) and in-use stability of the commercial product.

As amended, NDA 209529 is recommended for **Approval** from the drug product perspective. A 24-month expiration dating period for product when stored at the controlled room condition is granted. See attached IQA Chapter II, Drug Product, and associated memorandum, for additional discussion.

Environmental Assessment: Adequate

Quality Assessment #1, August 21, 2017, concluded that Astellas' request for a categorical exclusion from the requirement to prepare an

environmental assessment under 21 CFR § 25.31(b) could be granted based on the maximum expected introduction concentration (EIC) of solifenacin into the aquatic environment of 0.(b) (4) ppb (below the 1 ppb limit).

Because of the small NDO patient population, approval of the current indication is not expected to result in a significant increase in the use of solifenacin.

The acceptability of the claim for an exclusion from an EA was recently confirmed by Jim Laurenson, ONDP EA Team (see IQA Chapter II).

Labeling: Adequate

Quality Assessment #1, dated August 21, 2017, concluded that the labels and labeling were acceptable from the CMC perspective. Nevertheless, the August 28, 2017 Complete Response Letter included additional recommended revisions to the prescribing information (PI) and reference to previously proposed carton and container labels revisions that should be considered when resubmitting the application.

The draft PI submitted May 13, 2020 and the container and carton labels submitted on May 15, 2020 are acceptable from the CMC perspective. This NDA is recommended for **Approval** from the CMC labeling perspective (see attached IQA Chapter IV, Labeling Review). Note that the labeling (prescribing information, PPI) submitted on May 19, 2020, remains acceptable from the CMC perspective.

Note: The strength of VESIcare tablets, 5 mg and 10 mg, is based on the content of the active ingredient, solifenacin succinate. The VESIcare LS labeling retains the same basis for strength. This exception to the USP Salt Policy is consistent with MaPP 5021.1 Rev.1. The VESIcare LS labels and labeling include the required equivalency statement – 1 mg solifenacin succinate is equivalent to 0.75 mg solifenacin.

Manufacturing: Adequate

Process:
The manufacturing process detailed in the original submission and subsequent amendments, was found adequate from the Manufacturing Process perspective. The manufacturing process was not implicated in the OOS viscosity values for the finished product (see Quality Assessment #1, August 21, 2017).

The November 27, 2019 resubmission includes an updated batch formula, executed batch records for batches manufactured with the new formulation, and other supporting information. Other than a change to (b) (4) (b) (4) no other changes to commercial manufacturing process parameters have been made. After considering additional clarifying information subsequently provided by the Applicant, the OPMA Manufacturing Assessment team (i.e., Process and Facilities) has concluded that the manufacturing process is **Adequate**.

Facilities:
A Pre-Approval Inspection (PAI) of (b) (4), the commercial drug product manufacturing site, was performed on June 20 through 23, 2017. No FDA Form 483, Notice of Inspectional Observations, was issued at the inspection close-out. However, a facility 'Withhold' recommendation was issued because it was determined that the facility was not ready for the commercial manufacture of the drug product. The firm had failed to demonstrate that it could reliably manufacture the final drug product with the requisite quality attributes (e.g., viscosity) at a full scale commercial scale. To resolve this issue the firm needed to complete a root cause analysis, develop enhanced (b) (4) controls, and successful complete manufacture of process verification/validation batches.

Following resubmission of NDA 209529, a PAI of (b) (4) was requested due to the previous 'Withhold' recommendation. Because of travel restrictions due to the current pandemic, the PAI of the (b) (4) (b) (4) could not be completed as planned. Alternatives such as reliance on product 'Profile Class' history were considered. Although (b) (4) (b) (4) has manufacturing history for FDA-approved oral suspensions, because the 'Profile Class' for those products had not been updated from LIQ to SES, it was determined that reliance on 'Profile Class' history was unacceptable. As described in the attached Integrated Manufacturing Assessment (Chapter V), a "paper' inspection was conducted in accordance with the Sec. 704 (a)(4) (FDASIA Sec. 706) Records Request process. Documents were requested and reviewed by ORA and OPMA. After three rounds of this inspection process, ORA and OPMA now recommend approval of the (b) (4) site.

An overall manufacturing inspection recommendation of **APPROVE** was issued on May 8, 2020.

Biopharmaceutics: Adequate

The previously established dissolution test is performed using USP Apparatus 2, Paddles, at 50 rpm, and of 900 mL of 0.1 N HCl medium.

The acceptance criterion is NLT (b) (4)% (Q) dissolved at 15 minutes. (b) (4) (b) (4) (b) (4).

Because final commercial formulation reported in the resubmission differs from the phase 3 investigational product in (b) (4) (b) (4), comparative in vitro dissolution testing was conducted to bridge the two formulations.

Other than in 0.1 N HCl, where solifenacin is rapidly released precluding any comparison, multi-point dissolution testing in multiple, physiologic pH show similar release profiles from the two formulations. Therefore, this NDA is recommended **Approval** by the ONDP Division of Biopharmaceutics (see Chapter VI).

Microbiology (if applicable): Adequate

The August 21, 2017 Product Quality Microbiology assessment concluded that there were inadequate controls to ensure the absence of (b) (4) in the drug product at release and on stability.

As a product for oral administration it is not required to be sterile. However, it is expected to meet basic microbial limits requirements (total aerobic microbial count and total combined yeasts and molds count) and to be free of specified objectionable organisms (the specification includes a test to confirm the absence of *E. coli*). Although the drug product contains a methylparaben / propylparaben (b) (4), because this is an aqueous formulation it is susceptible to contamination (b) (4) (b) (4).

As documented in the November 27, 2019 resubmission and the January 12, 2020 amendment, controls for ensuring that the absence of (b) (4) have been established. The applicant has added a test and suitably validated analytical procedure for confirming the absence of (b) (4) in the finished product to the regulatory specification. The microbiology deficiencies identified in the Complete Response Letter have been **adequately** resolved (see IQA Chapter VII).

The combination of (b) (4), raw material controls, process and environmental controls, and testing at release and on stability, are adequate to ensure the microbiological quality of the drug product throughout its shelf-life and during the in-use period.

C. Risk Assessment

Risk Assessment Table (August 21, 2017 Quality Assessment)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Appearance	• Raw Materials • Formulation • Process • Stability	2	(b) (4)	Adequate	(b) (4)
Taste / Palatability	• Formulation • Raw materials • Process	32		Adequate	
Identification	• CGMPs	5		Adequate	
Assay (active) / Stability	• Formulation • Raw materials • Process • Container closure • Storage conditions	8		Adequate	
Related Substances Impurities / Degradants	• Formulation • Raw materials • Process • Container/Closure	18		Adequate	
Preservative Assay (Methylparaben and Propylparaben)	• Raw Materials • Process	24		Adequate	
Dissolution	• Formulation • Raw Materials • Process	2		Adequate	
pH	• Formulation • Raw Materials • Process	18		Adequate	
Microbial Limits	• Raw Materials • Formulation • Process	24		**Inadequate**	
Deliverable Volume	• Process parameters	1		Adequate	
Viscosity	• Raw Materials • Formulation • Process	18		**Inadequate**	
Redispersibility / Homogeneity	• Raw materials • Process	12		Pending resolution of viscosity issue	

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

Updated Risk Assessment

From Previous "Final' Risk Assessment			Resubmission Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Evaluation**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Microbial Limits	• Raw Materials • Formulation • Process	**Inadequate**	(b) (4)	Adequate	(b) (4)
Viscosity	• Raw Materials • Formulation • Process	**Inadequate**		Adequate	
Redispersibility / Homogeneity	• Raw materials • Process	Pending resolution of viscosity issue		Adequate	

^ Note that Astellas has not cited any (b) (4) Type IV DMFs for Carbomer Homopolymer Type CMC B. It is clear if (b) (4) (b) (4) (b) (4) active as of June 3, 2019, would apply. It is also unclear if (b) (4) (b) (4), closed December 31, 2019, fo (b) (4) would have been applicable.

* While the available data are very limited, it appears that (b) (4) (b) (4)

D. List of Deficiencies for Complete Response

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

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

N/A

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

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

N/A

***Application Technical Lead Name and Date**:*

Mark R. Seggel, Ph.D. May 26, 2020

{see electronic signature page}

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	Z. Ge, 06/13/17	
	Type III			N/A		
	Type IV			N/A		

N/A: There is sufficient information in the application, therefore the DMF did not need to be reviewed during the current review cycle.

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

Application Number	Document(s)	Description
IND 058135	Submissions and associated reviews	Solifenacin succinate
NDA 021518	Submissions and associated reviews, including drug substance CMC	VESIcare (solifenacin succinate) tablets, 5 mg and 10 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Nonclinical	N/A			
CDRH-OPEQ	N/A			
Clinical	N/A			
Other	N/A			

CHAPTERS: PRIMARY QUALITY ASSESSMENT

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (see Chapter II)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing Integrated Assessment

CHAPTER VI: Biopharmaceutics

CHAPTER VII: Microbiology

CHAPTER VIII: Additional Quality Disciplines (N/A)

########

Mark Seggel

Digitally signed by Mark Seggel
Date: 5/26/2020 02:55:59PM
GUID: 507572b5000036176969356148025bae

22 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **April 17, 2020**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch IV

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, ONDP/Division II/Branch IV

To: **Drug Product Review of NDA 209529 Resubmission**

Subject: **Review of Amendment 0040 for a New Viscosity Method**

Summary

After the NDA was recommended for Approval from the drug product perspective in the resubmission review, the OPMA reviewer informed the team that in the document submitted from the drug product manufacturer (b) (4), a new viscosity test (b) (4) was added to the specification (b) (4)). An information request was then sent to the applicant seeking clarification. In the amendment dated 16-April-2020, the applicant acknowledged that in addition to the current viscosity test specified in the NF monograph (b) (4) a test using (b) (4) (b) (4) has been established (b) (4) at the drug product manufacturing site. (b) (4) (b) (4) (b) (4). The acceptance criterion for the new method (b) (4) (b) (4) was established based on the (b) (4) finished drug product as shown in the following Figure.

The revised controls for the compendial excipients and [redacted] specification [redacted] are provided in the following Tables. The additional test for [redacted] viscosity provides better correlation with the finished drug product and therefore is acceptable.

Table 1 Excipients Used for Solifenacin Succinate Oral Suspension

Ingredient	Acceptance Criteria or Quality Standard
Polacrilin Potassium	NF
Methylparaben	NF
Propylparaben	NF
Propylene Glycol	USP
Simethicone Emulsion 30%	USP
Carbomer Homopolymer Type B	NF, [redacted]
Xylitol	NF
Acesulfame Potassium	NF
Natural Orange Flavor	[redacted]
Sodium Hydroxide	NF

NF: National Formulary; USP: United States Pharmacopeia

Table 2 [redacted] Specifications of Carbomer Homopolymer Type B

Test item	Test Method	Acceptance Criteria
Viscosity	USP <912> [redacted]	NLT [redacted] and NMT [redacted]

Recommendation:

The recommendation for the NDA remains to be **Approval** from the drug product perspective with 24 months of expiration dating period when stored at the controlled room condition.

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 4/17/2020 01:41:17PM
GUID: 508da7210002a030e76df4f60ccd142a

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/17/2020 01:55:05PM
GUID: 502d0913000029f9798ca689a802fa55

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **May 18, 2020**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch IV

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, ONDP/Division II/Branch IV

To: **Labeling Review of NDA 209529: Vesicare LS (solifenacin succinate) oral suspension**

Subject: **Final Recommendation for Labeling/Labels**

The labeling review #1 during the previous review cycle has recommended for Approval from CMC perspective. The draft PI proposed May 13, 2020 and carton label proposed on May 15, 2020, are acceptable from the CMC perspective.

Recommendation:

This NDA is recommended for **Approval** from the CMC labeling perspective.

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 5/18/2020 09:27:51AM
GUID: 508da7210002a030e76df4f60ccd142a

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 5/18/2020 09:37:50AM
GUID: 502d0913000029f9798ca689a802fa55

45 Pages have been Withheld in Full as B4(CCI/ TS) Immediately Following this Page

BIOPHARMACEUTICS REVIEW	
Application No.	NDA-209529-RESUB-33
Product Name	VESIcare LS (solifenacin succinate)
Applicant	Astellas Pharma US, Inc.
Dosage Form/Strength	Suspension, 1 mg/mL
Route of Administration	Oral
Indication	Treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older
Submission Date	11/27/2019
Primary Reviewer	Assadollah Noory, Ph. D.
Secondary Reviewer	Vidula Kolhatkar, Ph. D.
Recommendation	**ADEQUATE**

Background:

In the complete response letter issued on 8/28/2017 there was no direct deficiency listed for biopharmaceutics. In the biopharmaceutics' review dated 7/17/2017 the biopharmaceutics section of the NDA was found adequate and approval was recommended. However, the CR letter had a deficiency about quality of (b) (4). In order to address this deficiency related to the (b) (4) the applicant, in addition to submitting other information, (b) (4). The new formulation contains (b) (4) (b) (4) in formulation B used in phase 3 clinical trial, versus (b) (4) in the marketed pediatric formulation). The SUPAC guidance is silent regarding the level of change in (b) (4) components and composition. It was communicated to the Applicant that the change (b) (4) does not appear to be applicable to the proposed change (b) (4) in the drug product formulation. Therefore, use of in vitro dissolution data, and specifically multi-point profiles in multiple media, to support the proposed change was recommended (meeting minutes dated April 10, 2019). Thus, the Applicant submitted comparative dissolution data for formulation B (intended to-be-marketed formulation in the previous review cycle) and the pediatric commercial formulation (the currently proposed to-be-marketed formulation) in all physiologic pH dissolution media, see Appendix 2. The approved dissolution method and acceptance criterion are shown below.

USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criterion(a)
2	50	0.1N HCl at 37°C	900	NLT (b) (4)% (Q) at 15 minutes

Reviewer's Assessment:

The provided information meets the requirement of biopharmaceutics portion of the NDA. Although the similarity factor f2 cannot be calculated for the approved dissolution method the Applicant provided f2 values for all other dissolution media was requested, shown below.

Table 18 Results of f2 calculation of all test samples in each condition

Dissolution media	Lot Number of Reference drug product	f2 values of each test formulations				
		ZYBY	CBMMD	CBMNK	CBMNM	CBMNN
water	PVFM	overlapped [a]				
	ZGVM	overlapped [a]				
0.1N HCl	PVFM	Not less than (b)(4)% within 15 minutes [b]				
	ZGVM	Not less than (b)(4)% within 15 minutes [b]				
USP pH 4.5	PVFM	(b) (4)				
	ZGVM					
USP pH 6.5	PVFM					
	ZGVM					
USP pH 7.5	PVFM					
	ZGVM					

Test condition: USP apparatus 2, 50 rpm, 900 mL, 12 vessels

a: As the percent dissolved were low even at the infinity time point due to solifenacin-polacrilin complex characteristics, f2 value is not calculated

b: As the percent dissolved were not less than (b)(4)% within 15 minutes in both reference and test, evaluation of f2 value is not required.

The data shows that all batches show similar dissolution profile. The Applicant submitted adequate dissolution data to per the biopharmaceutics' recommendation for the NDA. Approval of this NDA is recommended by the division of biopharmaceutics.

Recommendation: **ADEQUATE**

From biopharmaceutics perspective this NDA is recommended for approval.

APPENDIX 1

Formulation

Table 1 Comparison of Formulations of Solifenacin Succinate Oral Suspension (Formulation A, Formulation B and Final Commercial Formulation)

Component	Function	Quantity in Formulation A (mg/mL)	Quantity in Formulation B (mg/mL)	Quantity in Final commercial formulation (mg/mL)
Solifenacin Succinate[1]	(b) (4)			
Polacrilin Potassium				
Methylparaben				
Propylparaben				
Propylene Glycol				
(b) (4)				
Simethicone Emulsion 30%				
(b) (4)				
Carbomer Homopolymer Type B				
Xylitol				
Acesulfame Potassium				
Natural Orange Flavor[2]				
(b) (4)				
Sodium Hydroxide				
Purified Water				

APPENDIX 1

Dissolution Data

Figure 6 **Dissolution profiles of Formulation B and final commercial formulation in five dissolution media**

(b) (4)

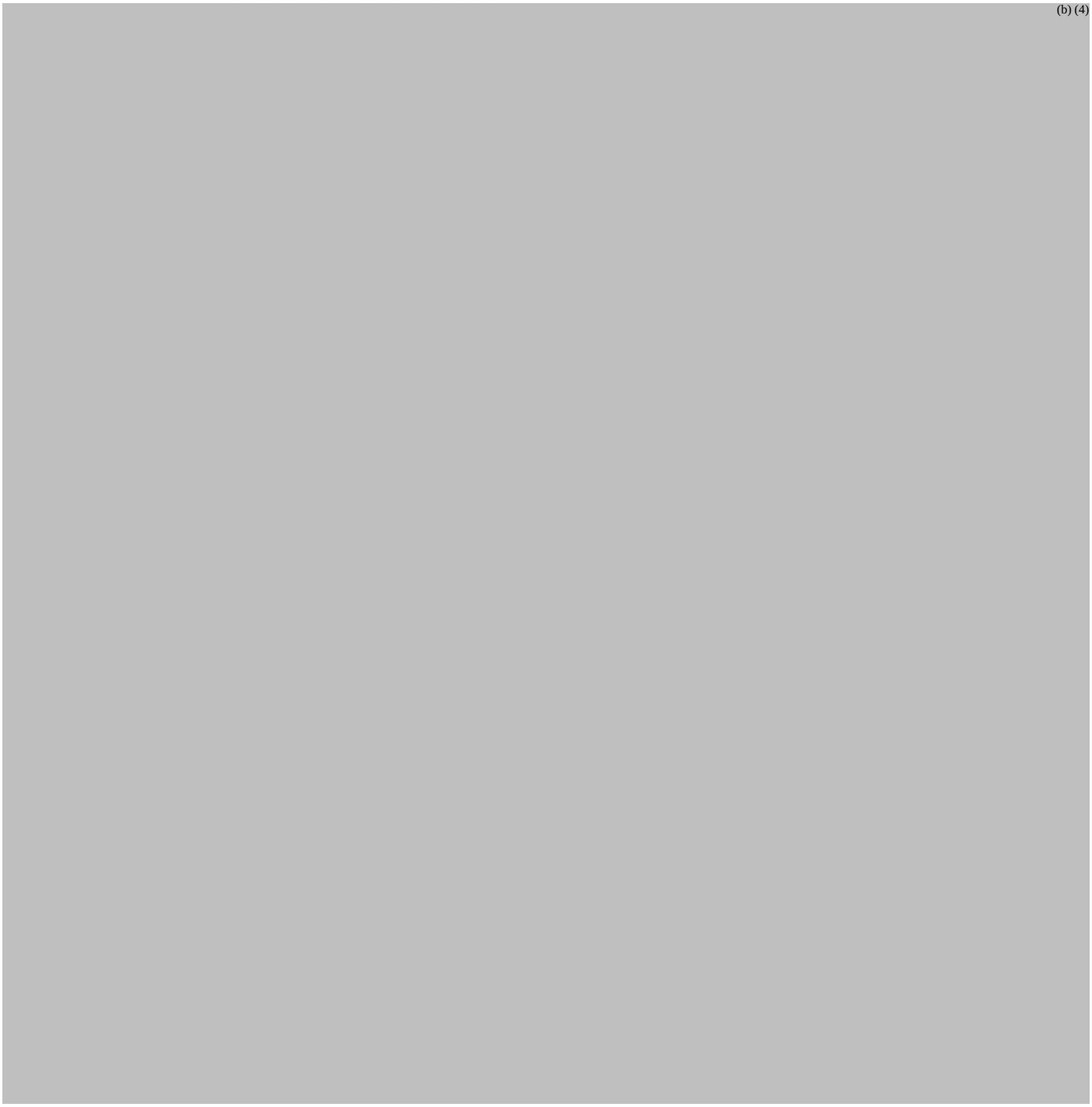
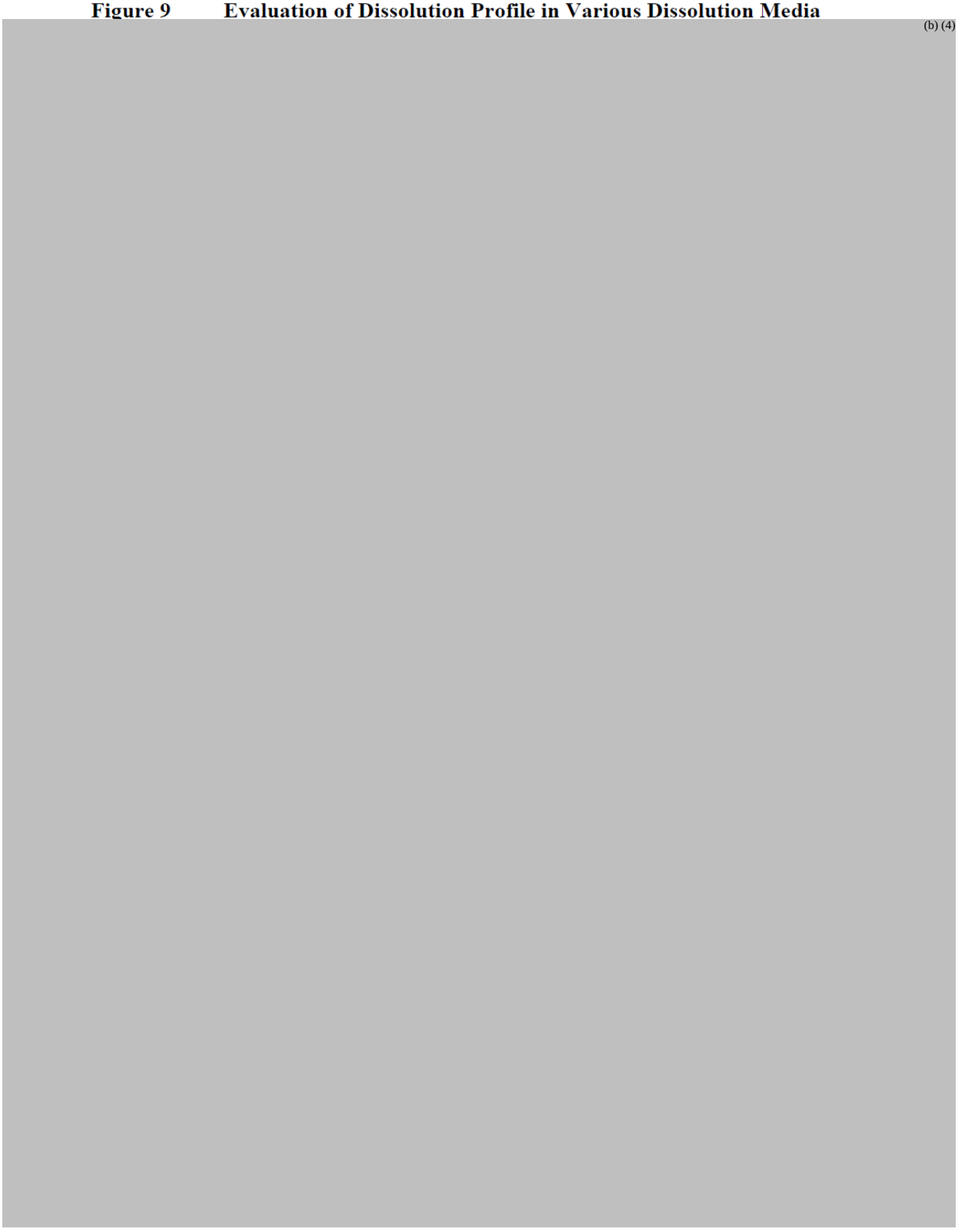


Figure 9 Evaluation of Dissolution Profile in Various Dissolution Media

(b) (4)



Assadollah Noory

Digitally signed by Assadollah Noory
Date: 4/01/2020 03:31:25PM
GUID: 508da6e000026b551cdd0c6e5c90e9f3
Comments: Hi Vidula, Would you like to approve this document Thanks, Assad

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 4/01/2020 04:07:03PM
GUID: 5424aeae00c3274f93e50573f7ca407e

MICROBIOLOGY

Product Background: Solifenacin succinate oral suspension (1 mg/mL) is supplied as a white to off-white suspension for oral use. 150 mL of the aqueous suspension is supplied in a (b) (4) (b) (4) bottle. It is a competitive muscarinic receptor antagonist indicated for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder (OAB) syndrome.

NDA: 209529

Drug Product Name / Strength: Solifenacin Succinate 1 mg/mL Oral Suspension

Route of Administration: Oral

Applicant Name: Astellas Pharma Global Development, Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: NA; the product is not sterile.

Review Summary:

General Overview of Deficiencies: N/A

List Submissions being reviewed:

Resubmission dated November 27th, 2019

An Information Request (IR) was issued by the Agency, dated January 3rd, 2020. The applicant's response, received January 14th, 2020, is addressed in the appropriate sections of this review.

Highlight Key Outstanding Issues from Last Cycle: Drug product specification for microbial limits, (b) (4) testing for microbial limits, post approval stability studies testing methods and specifications

Concise Description Outstanding Issues Remaining: N/A

Note to reviewer: The original submission for NDA 209529 was issued a Complete Response letter on August 28th, 2017. A Type B Pre-NDA Meeting Briefing was conducted and written responses to the outstanding issues were submitted via Preliminary Meeting Comments dated

04/09/2019. The following issues were covered in the original submission dated February 28th, 2017 and found to be adequate in microbiology review NDA209529MR01.pdf dated August 28th, 2017, they will not be covered further in this review: Description and Composition of Drug Product, Antimicrobial Effectiveness Testing, Manufacturers, and Package Insert. This document reviews the changes made in NDA 209529 Resubmission 33.

P.5 Control of Drug Product

P. 5.1 Specification

The following comments in italics were conveyed to the applicant during the Filing Communication dated April 24th, 2017:

Agency Microbiology Comment: *Your proposal to perform* (b) (4) *testing for the Microbial Limits test for drug product release is unacceptable because it does not comply with regulation (21 CFR 211.165 (a) and (b). If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the product release specification if adequate in process manufacturing controls tests and acceptance criteria provide assurance of the microbiological quality of each batch of the drug product are included. If you wish to omit the microbial limits specification, more information on the process is needed. Address the following points:*

a) Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product (purified water, simethicone emulsion 30%, natural orange flavor, etc.) and include microbial limits data for these critical raw materials.
b) Define the maximum processing time.
c) Describe microbiological monitoring and acceptance criteria for the critical control points which were identified. Verify the suitability of the proposed testing methods for the drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
d) Describe activities taken when microbiological acceptance criteria are not met at control points.

If you choose to omit microbial limits testing for release, then the microbial limits tests and acceptance criteria from the drug product release specification can be removed. Alternatively, a microbial limits specification for product release can be retained, but testing must be performed on every lot of drug product produced. Submit a revised drug product release specification for whichever microbial limits testing alternative is selected.

Sponsor response: In the response to the Filing Communication dated May 26th, 2017 the applicant agreed to (b) (4) test every batch.

The following comments in italics were conveyed to the applicant during the Filing Communication dated April 24th, 2017:

Agency Microbiology Comment: *Non-sterile aqueous drug products may potentially be contaminated with organisms* (b) (4) (b) (4) (b) (4) *Thus, despite the presence of otherwise adequate* (b) (4) *systems,* (b) (4) *can survive and even proliferate in product during storage. For a recent review of FDA's perspective on* (b) (4) (b) (4)

In order to control for the presence of (b) (4) *in your product you should consider the following:*

a) *Identify potential sources for introduction* (b) (4) *during the manufacturing process and describe the steps to minimize the risk* (b) (4) *in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.*

b) *Provide test methods and acceptance criteria to demonstrate the drug product is free of* (b) (4)*. Your test method should be validated, and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.*

As there are currently no compendial methods for detection of (b) (4) *we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting* (b) (4) *organisms would be adequate. It is currently sufficient to precondition representative strain(s) of* (b) (4) *n water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of* (b) (4) *Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.*

For more information, we refer you to Envir Microbiol 2011; 13(1):1-12 and J. Appl Microbiol 1997; 83(3):322-6.

Sponsor response: In the response to the Filing Communication concerning the presence of (b) (4) dated May 26th, 2017 applicant indicates the following: (b) (4) (b) (4) (b) (4) So the source of contamination of (b) (4) into the drug products is considered to be (b) (4). The applicant acknowledges the request to establish

appropriate controls for [(b) (4)] in the drug product and intends to provide test methods and acceptance criteria. The applicant considers that [(b) (4)] can be controlled under the acceptance criteria of TAMC ([(b) (4)] CFU/mL) by the microbial enumeration test as part of microbial limit testing that is already set in the final products specification, since [(b) (4)] is considered well detected and recovered by the test described in Section 3.2.P.5.2.8. To confirm this, the applicant will perform an additional validation study (i.e., the recovery study of multiple [(b) (4)] strains) of the microbial enumeration test.

Note to reviewer: The following deficiency language was included in microbiology review NDA209529MR01.pdf dated August 28th, 2017: "It is acknowledged that acceptable microbiological test methods and release specifications (TAMC microbial limit and *Escherichia coli*) are provided. Please revise the microbial limit release specification to include the test methods and acceptance criteria to demonstrate that the product is free of the objectionable microorganism [(b) (4)]. Additionally, in Quality Overall Summary Table 12 it still states, "Microbial limit test will be performed [(b) (4)] [(b) (4)]." Please provide an explanation and update the relevant sections of the submission as applicable."

<u>The following comments in italics were conveyed to the applicant during the Complete Response Letter dated August 28th, 2017:</u>
The drug product specification and post-approval stability program do not include the test methods and acceptance criteria to demonstrate that the product is free, and remains free, of the objectionable microorganisms in the [(b) (4)]

(11/27/19, 3.2.P.5.1, "3-2-p-5-1-specifications.pdf")

Specifications for Solifenacin Succinate Oral Suspension		
Test Items	**Test Methods**	**Acceptance Criteria**
[(b) (4)] assay	HPLC	Methylparaben: NLT [(b) (4)] and NMT [(b) (4)] mg/mL Propylparaben: NLT [(b) (4)] and NMT [(b) (4)] mg/mL
Microbial limit	USP <60>, <61>, <62>	TAMC: [(b) (4)] CFU/mL TYMC: [(b) (4)] CFU/mL *Escherichia coli*: absent [(b) (4)] [(b) (4)] absent [(b) (4)]
All tests will be performed on the primary packaged product.		

Batches (CBMNK, CBMNM, CBMNN) made for process validation conformed with specifications. (11/27/19, 3.2.P.5.4, "Batch Analyses.pdf", page 9-10/21)

Reviewer's Assessment: ***Adequate***
The applicant has added the absence of [(b) (4)] to the drug product specifications. Additionally, the applicant has committed to microbial limits testing on every batch and removed any reference to [(b) (4)]

P.5.2 Analytical Procedures

The following comments in italics were conveyed to the applicant during the Meeting Preliminary Comments April 9th, 2019:

Your planned response to the deficiencies includes changes to drug product specifications and post-approval stability programs to detect the presence of objectionable (b) (4) (b) (4) *organisms during manufacturing of the final drug product. In developing methods to address this deficiency, we recommend that you refer to the* (b) (4) (b) (4) *as an additional resource.*

(11/27/19, 3.2.P.5.2, "Analytical Procedures.pdf", page 14/14)

Microbial Enumeration Test

The applicant states they will perform tests as directed under 'Microbiological Examination of Non sterile Products', USP <60>, <61>, and <62>.

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

P.5.3 Validation of Analytical Procedures

(11/27/19, 3.2.P.5.2, "Analytical Procedures.pdf", page 40-43/43)

Microbial Enumeration Test

Microbial challenge test was performed to validate the microbial limit tests. To decrease the antimicrobial activity of the product, a (b) (4) dilution was employed for Total Aerobic Microbial Count (TAMC) and Total Combined Yeasts and Molds Count (TYMC). In the test for specific microorganisms (*E. coli* and (b) (4)) the drug product was diluted to 10 times with Soybean Casein Digest Broth, and 10 mL of the mixture was transferred into 90 mL of Soybean Casein Digest Broth and used for detection of specified microorganisms. Five test strains, *E. coli*, and three species of (b) (4) were used as the challenge microorganisms. All samples were dispensed in triplicate for each testing.

TAMC Microbial Enumeration Test Results					
Test strain	**Inoculum count (CFU)**	**Positive control (CFU)**	**Sample count (CFU)**	**% Recovery (control vs. inoculum)**	**% Recovery (sample vs. control)**
(b) (4)					

(b) (4)

TYMC Microbial Enumeration Test Results					
Test strain	**Inoculum count (CFU)**	**Positive control (CFU)**	**Sample count (CFU)**	**% Recovery (control vs. inoculum)**	**% Recovery (sample vs. control)**
(b) (4)					

Specific Microorganism (*E. coli*) Detection Test Results				
Test strain	**Inoculum count (CFU)**	**Recovery media**	**Control**	**Sample**
(b) (4)				

Specific Microorganism (b) (4) Detection Test Results				
Test strain	**Inoculum count (CFU)**	**Recovery media**	**Control**	**Sample**
(b) (4)				

The following comments in italics were conveyed to the applicant during an Information Request dated January 3rd, 2020:

Agency Microbiology Comment: *In the submission dated 11/27/19, section 3.2.P.5.3, "Analytical Procedures.pdf", pages 40-43/43, regarding the method suitability/validation of the Microbial Enumeration Test used for testing drug product specifications during routine commercial production, please provide information of a protocol to demonstrate compliance with USP <60> specifically addressing the following:*

a. Validation studies demonstrate the capability of the test methods to grow microorganisms during testing however, there was no information on the incubation times and conditions used.

b. In the tests for specific microorganism there was no information on the methods used to identify the colonies to detect the presence of objectionable organisms (b) (4)

Sponsor response: In the response to the Information Request concerning the presence of (b) (4) dated January 14th, 2020 the applicant responded with the following:

Suitability of the test method was confirmed completely in accordance with USP <60>. Please find the requested responses below and additional detail provided in the attached verification report.

a. The incubation times and conditions follow USP <60>: i.e., the pre-incubation time in Soybean-Casein Digest Broth (SCDB) was not more than 48 hours and the incubation time for selection and subculture on (b) (4) was also not more than 48 hours as shown in Table 1.

Table 1 Incubation times and conditions used for the suitability of the test method

Culture media	Temperature	Incubation time
SCDB	30-35°C	Approx. 47 hours
(b) (4)	30-35°C	Approx. 44 hours
SCDB: Soybean-Casein Digest Broth, (b) (4)		

b. Three types of pure culture of (b) (4) which have been identified and confirmed by identification system (i.e., (b) (4) by MIDI system based on fatty acid analysis and by genetic identification by (b) (4) (b) (4) were challenged into the control (mixture of phosphate buffer pH 7.2 and SCDB) and sample solutions, respectively. Both positive control and sample with (b) (4) showed the same indication reactions whereas negative control did not show any growth, indicating that the colonies observed on (b) (4). Moreover, the appearance of the colonies was inspected by visual observation to be pure cultures and the result that the morphological characteristics of the colonies were (b) (4) (b) (4) which are the typical indication reactions noted in USP <60>, supported the presence of the (b) (4).

Note to reviewer: Incubation times were included for validation studies and appear reasonable to promote the growth of (b) (4) Additionally, the applicant acknowledged that challenge organisms presented the same indication reactions for sample and positive control. Furthermore, the colonies were identified through macroscopic inspections to be pure cultures with morphological characteristics typical of (b) (4).

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

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(11/27/19, 1.14.1.3, "Draft Labeling Text [PDF].pdf", page 12/16)
Solifenacin Succinate 1 mg/mL Oral Suspension is stored at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F-86°F) [See USP Controlled Room Temperature]. Discard any unused product 28 days after opening the bottle.

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

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Note to reviewer: The following deficiency language was included in microbiology review NDA209529MR01.pdf dated August 28th, 2017: "Please revise the post approval stability program to include testing and specifications to confirm the absence of (b) (4)."

The following comments in italics were conveyed to the applicant during the Complete Response Letter dated August 28th, 2017:
The drug product specification and post-approval stability program do not include the test methods and acceptance criteria to demonstrate that the product is free, and remains free, of the objectionable microorganisms (b) (4)

(11/27/19, 3.2.P.8.2, "Post-approval Stability Protocol and Stability Commitment.pdf")

At least one batch per year of Solifenacin succinate oral suspension will be placed in a long term stability study with yearly monitoring. The annual stability will be only applicable for those years in which a batch is produced for commercial use. Marketed batches found to be out of specifications during the expected shelf life will be reported to the Agency as required under 21 CFR 314.81(b)(1)(ii) and the necessary actions will be taken.

Stability Protocol for Annual Stability of Solifenacin Succinate Oral Suspension							
Conditions	**Test**	**Time (Months)**					
		0	**3**	**6**	**12**	**24**	**36***
Long Term 25° ± 2°C/60% ± 5% RH	Preservative Assay	X	X	X	X	X	X
	Microbial Limit Test	X			X	X	X
*Optional							

Reviewer's Assessment: ***Adequate***
The applicant has added the absence of (b) (4) to the drug product specifications.

P.8.3 Stability Data

Stability Specifications:
Methylparaben (b) (4)
Propylparaben (b) (4)
Microbial Limit will conform to drug product specifications (including absence of (b) (4)) (11/27/19, 3.2.P.2.5, "3.2.P.2.5 Microbiological Attributes.pdf", page 4/4)

(11/27/19, 3.2.P.8.3, "Stability Data.pdf", page 81-82/82)
Validation of Analytical Method for (b) (4):
The validation studies were performed to detect the presence of (b) (4). Three representative species were suspended in water and incubated at 20-25°C for 4 days then challenged to the test system. Recovery of (b) (4) in the presence of product was confirmed using the shortest incubation period of the test method.

Specific Microorganism (b) (4) Detection Test Results				
Test strain	**Inoculum count (CFU)**	**Recovery media**	**Control**	**Sample**
(b) (4)				

Note to reviewer: (b) (4) detection validation was performed for microbial limit drug product testing, using (b) (4) Although not specifically indicated in the submission, this reviewer assumes these older tests were performed using MacConkey Agar to validate the testing methods since this predates the publication of USP <60>

Long-term Stability Studies (25°± 2°C/ 60% ± 5% RH)
(11/27/19, 3.2.P.8.3, "Stability Data.pdf", page 29-31/82)

All lots tested (CBMNK, CBMNM, CBMNN) met specifications for Microbial Limits when tested at initial and 6 months (12 and 24-month study is "to be tested").

All lots tested (CBMNK, CBMNM, CBMNN) met specifications for (b) (4) assay (methylparaben and propylparaben) when tested at initial, 3, and 6 months (12 and 24-month study is "to be tested").

Long-term Stability Studies (40 ± 2 °C/75 ± 5%RH)
(11/27/19, 3.2.P.8.3, "Stability Data.pdf", page 32-34/82)

All lots tested (CBMNK, CBMNM, CBMNN) met specifications for (b) (4) assay (methylparaben and propylparaben) when tested at initial, 1, 3, and 6 months (12 and 24-month study is "to be tested").

Antimicrobial Effectiveness Testing at Expiry
(11/27/19, 3.2.P.2.5, "3.2.P.2.5 Microbiological Attributes.pdf", page 1-2/4)

The applicant conducted antimicrobial effectiveness testing at expiry for the following non-commercial batches *FSHB, FSHC, FSHD, KVHX, MKWK, MFBC, MFBD, MFBF, NFHK, PKYT, PVFM, PVFN, and PVFP. The applicant states that all tested batches passed AET according to USP <51>.
*Batch size of (b) (4) instead of (b) (4) for routine commercial production.

Note to Reviewer: Long term and Accelerated stability studies conform with drug product specifications. The applicant also demonstrated that antimicrobial effectiveness is maintained through the storage period.

The following comments in italics were conveyed to the applicant during an Information Request dated January 3rd, 2020:
Agency Microbiology Comment: *Regarding Stability Studies in the submission dated 11/27/19, section 3.2.P.8.3, "Stability Data.pdf", pages 81-82/82 under Validation of the Analytical Method for Specified Microorganisms (* (b) (4) *please provide information or a protocol to demonstrate suitability of test conditions and compliance with USP <60> specifically addressing the following:*

a. The incubation conditions for the preconditioning of (b) (4) *is noted however, there is no information on the incubation times and conditions used with the MacConkey Agar.*

b. Please describe if and how the challenge organisms were combined with drug product, diluted or otherwise during validation studies.

c. While the results of the validation demonstrated growth, there was no information on the methods used to identify the colonies to confirm the presence of objectionable organisms (b) (4)

Sponsor response: In the response to the Information Request concerning the presence of (b) (4) dated January 14th, 2020 the applicant responded with the following:
Suitability of the original test method was established based on the advice in the letter issued on 24 April 2017 during the original NDA review, prior to the effective date of USP<60>. Please

find the requested responses below and additional detail provided in the attached validation report. Please be informed that test for specified microorganisms (b) (4) in the primary stability study (PSS) will be continued with the test method described in CTD module 3.2.P.5.2 (i.e., according to the USP <60>) from the next sampling point. Further, the retained samples for initial and 6 months sampling points for the PSS batches will also be tested according to USP <60> retrospectively.

a. The incubation times and conditions used for suitability of the test method conducted at (b) (4) are shown in Table 2. The 18 hours incubation times for enrichment culture in SCDB and for selection and subculture on MacConkey Agar (MacA) were determined in reference to those for *Escherichia coli* in the harmonized method (general test JP 4.05, USP <62>, and Ph. Eur. 2.6.13). The suitability of the incubation times was confirmed in the bacterial challenge tests; therefore, the incubation times in SCDB for 18-24 hours and on MacA for 18-72 hours were set in the test method.

Table 1 Incubation times and conditions used for the suitability of the test method

Culture media	Temperature	Incubation time
SCDB	30-35°C	18 hours
MacA	30-35°C	18 hours

SCDB: Soybean-Casein Digest Broth, MacA: MacConkey Agar

b. Into 90 mL of SCDB, 10 mL of 1:10 sample solution corresponding to 1 mL of the product was transferred to make 1:100 diluted enrichment culture broth. And then 0.1 mL of (b) (4) test microbial suspension* (i (b) (4)) which contains not more than (b) (4) CFU/mL was added to make inoculated enrichment culture broth, respectively.

*Each (b) (4) were separately suspended in water and were incubated at 20-25°C for 4 days in order to prepare (b) (4) test microbial suspension acclimated to the conditions in the manufacturing environment.

c. Three types of (b) (4) were challenged into control (SCDB) and sample solution, respectively. In addition, both positive control and sample with (b) (4) showed the same indication reactions whereas sample control and negative control did not show any growth, indicating that the colonies observed on MacA are the (b) (4). Moreover, the appearance of the colonies was inspected by visual observation and the result that the morphological characteristics of the colonies were (b) (4) supports the presence of the (b) (4).

Note to reviewer: Incubation times and conditions were included for stability studies and appear reasonable to promote the growth of (b) (4). Moreover, the applicant agrees for future stability studies and all future batch stability studies to test according to the (b) (4) methods described in Section 3.2.P.5.2 (reviewed above). The applicant identifies how the drug product was added to the culture media and how the challenge organism positive control was made during stability studies. Lastly, the applicant acknowledged the challenge organisms presented the same indication reactions for sample and positive control and the colonies were identified through macroscopic inspection to be pure cultures with morphological characteristics typical of (b) (4)

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

R REGIONAL INFORMATION

R.1 Executed Batch Record

Executed Batch Records of Primary Stability Batches		
Date	**Scale (L)**	**Lot #**
February 2019	(b) (4)	CBMNK
February 2019		CBMNM
February 2019		CBMNN

R.2 Comparability Protocol – No CP was included in the application.

NDA: 209529 APPLICANT: Astellas Pharma Global Development, Inc.

DRUG PRODUCT: Solifenacin Succinate 1 mg/mL Oral Suspension

List of Deficiencies: *N/A*

Primary Microbiology Reviewer Name and Date:

Andrew P. Brown, Ph.D.
Microbiologist
CDER/OPQ/OPMA/DMA II/Branch 5
1/31/2020

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

Nandini Bhattacharya, Ph. D.
Quality Assessment Lead (Acting)
CDER/OPQ/OPMA/DMA II/Branch 5
1/31/2020

Andrew P Brown (OPQ)

Digitally signed by Andrew P Brown (OPQ)
Date: 2/07/2020 11:24:04AM
GUID: 5858433a0010647aeb8e5b6e407f7f99

Nandini Bhattacharya

Digitally signed by Nandini Bhattacharya
Date: 2/07/2020 12:50:24PM
GUID: 508da70c00028f454473851fced0e9d4

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARK R SEGGEL
05/26/2020 03:20:27 PM

Recommendation: ***As of this review, this 505(b)(1) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(1) and 314.125(b)(13).***

NDA 209529

VESIcare LS (solifenacin succinate oral suspension)

Review #1

Drug Name/Dosage Form	Solifenacin Succinate Oral Suspension
Strength	1 mg/mL (equivalent to 0.75 mg solifenacin per mL)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Astellas Pharma US, Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (0000)	02/28/17	All
0014	05/17/17	Product
0017	05/26/17	Product, Micro, Biopharm, Process
0019	05/31/17	Product
0020	06/05/17	Product, Micro, Biopharm, Process
0025	06/28/17	Product, Micro, Biopharm, Process
0027	07/12/17	Product, Micro, Biopharm, Process, Facilities
0028	07/19/17	Product, Micro, Biopharm, Process, Facilities
0029	07/31/17	Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Debasis Ghosh	OPQ/ONDP/DNDPAPI/BII
Drug Product	Zhengfang Ge	OPQ/ONDP/DNDPII/BV
Process	James Norman/Jean Tang	OPQ/OPF/DPAII/BV

Microbiology	Andrew Brown	OPQ/OPF/DMA/BII
Facility	Krishnakali Ghosh	OPQ/OPF/DIA/BIII
Biopharmaceutics	Ho-pi Lin	OPQ/ONDP/DB/BBIII
Regulatory Business Process Manager	Thao Vu	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Mark Seggel	OPQ/ONDP/DNDPII/BV
Laboratory (OTR)	-	-
ORA Lead	-	-
Environmental	Zhengfang Ge	OPQ/OPF/DPAI/BII

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	Z. Ge, 06/13/17	
	Type III			N/A		
	Type IV			N/A		

N/A: 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
Submissions and associated reviews	IND 058135	Solifenacin succinate
Submissions and associated reviews, including drug substance CMC	NDA 021518	VESIcare (solifenacin succinate tablets), 5 mg and 10 mg

2. CONSULTS

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

na Not Applicable

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, Astellas Pharma's 505(b)(1) New Drug Application #209529, for VESIcare LS (solifenacin succinate) oral suspension, 1 mg/mL, is not ready for approval.

As observed during the inspection of the drug product manufacturing facility, and as described in amendments to the NDA, drug product that meets the proposed drug product specification, and in particular the requirements for product viscosity, currently cannot be manufactured. As a result of changes in the manufacture of (b) (4) (b) (4), drug product viscosity now falls below the established lower limit. The applicant is evaluating additional raw material controls that will identify (b) (4) suitable for use in the manufacture of VESIcare LS.

While the available data are very limited, it appears that (b) (4) (b) (4) Nevertheless, from both the drug product and facilities review perspectives, this application cannot be recommended for approval until adequate controls for (b) (4) (b) (4) are established, and the applicant has demonstrated that drug product with the requisite quality can be manufactured consistently.

The product quality microbiology review team has determined that there are inadequate controls to ensure the absence of (b) (4) in the drug product at release and on stability. The application cannot be approved until this issue is addressed by the applicant.

Adequate drug substance and product manufacturing process information has been provided. And, from the biopharmaceutics perspective, suitable controls for *in vitro* dissolution have been established. In its present form the labeling (package insert, container/carton) is acceptable from the CMC perspective. However, because labeling negotiations have not been completed, the adequacy of the labeling will need to be confirmed when the NDA is resubmitted.

See Attachment II of this review for a list of deficiencies to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Solifenacin succinate oral suspension, 1 mg/mL, is indicated for the treatment of pediatric patients aged 2 years and older with neurogenic detrusor overactivity (NDO).
Duration of Treatment	Indefinite.
Maximum Daily Dose	Up to 10 mg solifenacin succinate per day.
Alternative Methods of Administration	Not applicable.

VESIcare (solifenacin succinate) tablets, 5 mg and 10 mg, was approved under Astellas' NDA 21518 on November 19, 2004. VESIcare is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. Solifenacin succinate oral suspension, 1 mg/mL, was developed for the treatment of pediatric patients aged 2 years and older with neurogenic detrusor overactivity (NDO). While not an NME, this application will be a Priority because of the potentially significant utility in the treatment of pediatric patients with overactive bladder resulting from a neurologic lesion. In this population, the most common cause of NDO is a congenital neural tube defect.

B. Quality Assessment Overview

Drug Substance

Solifenacin succinate is a water soluble (610 mg/mL) antimuscarinic agent with high affinity for muscarinic M_3-receptors. The chemistry, manufacturing and controls (CMC) for solifenacin succinate are documented in Astellas' NDA 21518 for solifenacin succinate tablets which was approved on November 19, 2004. There are no outstanding issues associated with the drug substance CMC. NDA 209529 is thus recommended for approval from the drug substance review perspective.

Drug Product

Solifenacin succinate oral suspension, 1 mg/mL contains the equivalent of 0.75 mg/mL solifenacin. The proposed daily dose is weight based and ranges from 2 mL to 10 mL. The dose is administered once daily using an oral syringe and bottle adaptor supplied by the dispensing pharmacy.

Inactive ingredients in the aqueous suspension include Polacrilin Potassium, NF, [redacted]. Other components include Carbomer Homopolymer Type B, NF [redacted] methylparaben and propylparaben, [redacted] natural orange flavor, propylene glycol, and [redacted] sodium hydroxide. [redacted]

The drug product is filled to a volume of 150 mL in amber polyethylene terephthalate bottles with polyethylene / polypropylene child-resistant caps. [redacted]. The bottle material (PETE) is of suitable quality for storage of an aqueous suspension.

The drug product specification includes the tests to ensure the identity, strength, quality, purity potency and bioavailability of the drug products. Identity is confirmed by HPLC retention time and UV spectrum. Solifenacin assay is controlled to [redacted]% of the label claimed. Related substances (degradation products) in the drug product are controlled at the same limits as in VESIcare Tablets. Microbial limits testing and preservative assay are discussed under Microbiology.

Solifenacin-polacrilin complex particle size does not change significantly on stability. Such charged particles are not expected to aggregate. [redacted] control for particle size is adequate. Content uniformity (bottle to bottle consistency) is assured via [redacted] testing and is therefore not included in the product specification.

The drug product specification also includes tests for pH (NLT [redacted] and NMT [redacted]) and for viscosity [redacted]

Product viscosity is considered important [redacted] for maintaining product homogeneity and dose uniformity. A minimum viscosity of [redacted] was shown to be sufficient to maintain product uniformity. [redacted] supplied by [redacted] is the critical component for establishing product viscosity.

Product batches used in the clinical trials and registration stability studies, as well as the validation batches manufactured by [redacted] prior to 2015 met all product test requirements including viscosity. However, during the manufacture of commercial launch materials for the European Union, out-of-specification (OOS) results for product viscosity [redacted] were observed. The first of these batches had been manufactured in 2015. The OOS investigation was reported to the FDA in early June 2017 and prior to the pre-approval inspection of [redacted] scheduled for later that month. Because the U.S. clinical, stability and validation batches had been manufactured

successfully, the significance of these OOS observations was not fully appreciated. It was only after the June 20 to June 23, 2017 pre-approval inspection of (b) (4) that the extent of the problem was understood. We subsequently requested additional information from Astellas.

The product viscosity failures occur at (b) (4) and have been attributed to a change in the manufacture of (b) (4) by (b) (4) While the new lots (b) (4) were manufactured within validated process ranges and the materials continued to meet the USP/NF monograph requirements for (b) (4). However, in Astellas' application of the material at a level of (b) (4) the material no longer functions as required. (b) (4) (b) (4).

Investigations are ongoing and are focused on identifying quality attributes of (b) (4) (b) (4) that can be used to distinguish between different lots of (b) (4). Astellas does not anticipate completing this work, which will include demonstrating that product can be consistently manufactured with the requisite viscosity, until the end of October 2017, which is well after the PDUFA goal date of August 28, 2017.

At our request, Astellas has characterized to the impact of OOS viscosity on product homogeneity. The data, albeit very limited, suggests that even with a viscosity as low as (b) (4) only minimal shaking is required to ensure product homogeneity and dose uniformity. It is unclear at what viscosity product homogeneity would be adversely impacted. Nor is clear why Astellas has not proposed revising the lower limit for product viscosity.

Until this issue is resolved by establishing additional raw material controls for incoming lots of (b) (4) and otherwise demonstrating that drug product with the requisite viscosity (and therefore homogeneity and dose uniformity) can be consistently manufactured, this NDA is not recommended for approval.

Stability data from the primary stability / registration batches (manufactured with original (b) (4) were obtained at 25°C/60% RH over 36 months and at 40°C/75% RH over 6 months. Temperature cycling and in-use stability studies were also conducted While no significant trends in product quality were observed, Astellas has nevertheless proposed an expiration dating period of only 24 months when stored in the original bottle at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F-86°F) [see USP Controlled Room Temperature]. Unused product should be discarded 28 days after opening the bottle. Shelf-life considerations may need to be re-evaluated depending on how the (b) (4) product viscosity issue is resolved.

Analytical methods verification by FDA's St. Louis laboratory was not requested. The drug is not an NME and the procedures are relatively straight forward and make use of common techniques (e.g., HPLC).

Environmental Assessment

The applicant has requested a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b). Astellas does not anticipate that approval of this NDA for the NDO indication will significantly increase the expected introduction concentration (EIC) of solifenacin into the aquatic environment. The maximum level resulting from the combined use of VESIcare and VESIcare LS over any of the next 5 years is not expected to exceed (b) (4) ppb, which is well below the 1 ppb threshold. Astellas states that there are no extraordinary circumstances associated with the use of solifenacin succinate. The categorical exclusion is therefore granted.

Labeling

VESIcare LS (solifenacin succinate oral suspension labeling consists of a package insert, a bottle label and a carton label. The CMC-related sections have been reviewed, and in collaboration with DMEPA, recommendations have been conveyed to the applicant.

Revisions include addition of a salt equivalency statement ("1 mg solifenacin succinate is equivalent to 0.75 mg solifenacin active moiety"), and expression of the dose strength as 5 mg / 5 mL rather than 1 mg / mL. Overall, as revised the labeling contains the necessary information required under 21 CFR 201.

The proposed proprietary name for the oral suspension is VESIcare LS, where LS stands for liquid suspension. Despite initial concerns with the use of the extension LS, the review team (DBRUP, DMEPA, OPQ) finds the name acceptable.

Although the current labeling is acceptable, additional revisions may be warranted during review of the resubmission. For example, the labeling currently states to shake the bottle (b) (4) prior to each administration. Recently submitted data indicates that shaking the bottle well is sufficient to ensure homogeneity and dose uniformity. The labeling currently states, "Store in original bottle" and " (b) (4) Dispense in a tight light resistant container (b) (4) ." The product should be stored in the original bottle and should not be transferred to another container for dispensing.

Process

The drug product manufacturing process involves (b) (4)
(b) (4)
(b) (4) Adequate (b) (4) controls have been established.

Phase 3 batches were manufactured at the (b) (4) scale and process validation batches were manufactured at the (b) (4) scale. The process review team notes that, "Batches

consistently met specification until a vendor changed the quality of a viscosity enhancer used in this process. Since the manufacturing process is not implicated in the OOS viscosity values for the finished products, the process remains adequate." The application is recommended for approval from the drug product manufacturing process review team's perspective.

Facilities

The two Astellas facilities associated with drug substance manufacturing were found acceptable based on file review. Note that these are the same facilities used for the manufacture of API used in the manufacture of VESIcare (solifenacn succinate tablets)

A Pre-Approval Inspection (PAI) of the drug product manufacturing site, (b) (4) (b) (4)) was conducted June 20 to June 23, 2017. As discussed above, (b) (4) has been unable to successfully manufacture the drug product for commercial launch in the EU (or to support the US launch) due to failing product viscosity. As discussed above the viscosity failure has been linked to changes in the manufacture of (b) (4). An investigation into the failures is ongoing. Work with the excipient vendor and an external testing laboratory is also ongoing. Although an FDA Form 483 was not issued at the inspection closeout, (b) (4) was advised that a withhold recommendation would be made. Two other (b) (4) facilities have acceptable CGMP status based on file review.

The Division of Inspectional Assessment (OPQ/OPF/DIA) review team states that, "the firm (b) (4) has failed to demonstrate that it can reliably manufacture the final drug product Solifenacin Succinate Suspension at a commercial scale and meet its quality attributes and hence a facility withhold has been recommended." An Overall Application Recommendation of Withhold has been issued.

Note that re-inspection of (b) (4) will probably not be requested, although summary data and validation reports will be reviewed upon submission of the applicant's response to the CR letter.

Biopharmaceutics

Solifenacin succinate is highly water soluble. (b) (4) (b) (4) (b) (4) In vitro release testing as part of the quality control program is performed using USP apparatus II (paddle) at 50 rpm and dissolution medium of 900 mL of 0.1 N HCl at 37°C. An acceptance criterion of Q = (b) (4)% of the label claim dissolved (b) (4) in 15 minutes has been established. From the Biopharmaceutics perspective the application is recommended for approval.

Microbiology

Solifenacin succinate oral suspension is a non-sterile aqueous-based liquid for oral administration. While the product is not required to be sterile, it is manufactured in a manner and environment designed to minimize microbial contamination. In addition, a methylparaben / propylparaben (b) (4) is present to prevent microbial growth during storage and during the in-use period, when the bottle will be repeatedly opened. Antimicrobial preservative effectiveness testing has demonstrated the efficacy of antimicrobial preservation throughout the shelf-life of the product.

The proposed drug product specification includes a test for the assay of methylparaben and propylparaben, and tests for microbial limits in accordance with USP<1111>. Tests for total aerobic microbial content (TAMC), total yeasts and mold content (TYMC) and the absence of *E. coli* follow USP<61> and USP<62>. Astellas proposed (b) (4) testing (b) (4) with respect to microbial limits, but at the request of the microbiology review team, Astellas has agreed to perform microbial limits testing on every batch.

Astellas was advised that, "Non-sterile aqueous drug products may potentially be contaminated with organisms in the (b) (4) strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, (b) (4) strains can survive and even proliferate in product during storage." Astellas was also advised to "provide test methods and acceptance criteria to demonstrate that the drug product is free of (b) (4)". However, Astellas has only proposed to control (b) (4) under the acceptance criteria for TAMC ((b) (4) CFU/mL). This is unacceptable from the product quality microbiology perspective; the applicant must demonstrate absence of (b) (4) in the drug product at release and on stability.

Therefore, from the product quality microbiology perspective the application in its current form is not recommended for approval.

C. Special Product Quality Labeling Recommendations

There are no special product quality labeling recommendations at this time.

D. Final Risk Assessment (see Attachment 1)

E. List of Deficiencies for Complete Response

The following list of deficiencies is taken directly from the IQA chapters. This list is followed by revised draft text for the Complete Response Letter.

A. Drug Substance Deficiencies

Not Applicable

B. Drug Product Deficiencies

The quality of [redacted] is not sufficiently controlled. Therefore, the recent drug product batches, manufactured with [redacted] after the supplier changed the manufacturing process, failed the product specification.

Not sufficient drug product batch data are provided to assure the homogeneity of the drug product manufactured with the new [redacted] to ensure the dosing accuracy

To address these deficiencies, the applicant should meet the following requirement and provide batch release data from three drug product batches manufactured with the new [redacted]:

• Propose an extra control of [redacted] in addition to NF monograph to assure that the drug product meets the specification
Or
• Include a [redacted] test in the drug product specification to assure the homogeneity of the drug product [redacted]. This test should be performed at the drug product release and during the stability testing

C. Environmental Deficiencies

Not Applicable

D. Labeling Deficiencies

Not Applicable

E. Process Deficiencies

Not Applicable

F. Facilities Deficiencies

During a recent inspection of [redacted] manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA

may be approved. [*Note: This is standard language and cannot be modified.*]

G. Biopharmaceutics Deficiencies

Not Applicable

H. Microbiology Deficiencies

a. For release specifications in P.5.1, it is acknowledged that acceptable microbiological test methods and release specifications (TAMC microbial limit and Escherichia coli) are provided. Please revise the microbial limit release specification to include the test methods and acceptance criteria to demonstrate that the product is free of the objectionable microorganism (b) (4) Additionally, in Quality Overall Summary Table 12 it still states "Microbial limit test will be performed (b) (4) (b) (4) Please provide an explanation and update the relevant sections of the submission as applicable.

b. Please revise the post approval stability program to include testing and specifications to confirm the absence of (b) (4)

c. During stability studies the results of the microbial limit test should comply with the acceptance criteria which includes the absence of (b) (4) (b) (4)

I. Other Deficiencies (specify discipline)

Not Applicable

Draft Text for Complete Response Letter

Deficiencies:

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

2. The quality of (b) (4) as currently supplied by (b) (4) is not adequately controlled, resulting in drug product batches that do not meet the proposed drug product specification.

3. The drug product specification and post-approval stability program do not include the test methods and acceptance criteria to demonstrate that the product is free, and remains free, of the objectionable microorganisms in the (b) (4)

Information Needed to Address the Deficiencies:

To address the first two deficiencies, submit the following information:

• Results from the ongoing [redacted] characterization studies, including a summary of your investigations and the corrective and preventive actions taken to address the root cause.
• Establish and validate additional tests and acceptance criteria for [redacted]
• Batch analyses from three verification/validation batches demonstrating that drug product manufactured with [redacted] meeting the NF and additional quality requirements, has the requisite quality (e.g., viscosity). Include executed batch records from the validation batches along with the validation protocol and the final summary report.

If suitable additional controls for [redacted] cannot be identified and validated or if [redacted] is unable to supply [redacted], [redacted] meeting the enhanced raw material specification, revision of the acceptance criteria for drug product viscosity may be proposed. Along with a justification for revising the lower limit, confirm, with release and stability data, that drug product quality and performance, including homogeneity, is not adversely impacted.

To address the third deficiency,

• Revise the drug product specification to include the test method(s) and acceptance criteria to assure that the product is free of the objectionable microorganisms in the [redacted]. Update the relevant sections of the application accordingly.

• Revise the post-approval stability program to include testing to confirm the absence of [redacted].

Additional Comments:

Update Table 12, Specifications for Solifenacin Succinate Oral Suspension (module 2.3.P Drug Product Quality Overall Summary), to reflect that the microbial limit tests will be performed on every batch.

Application Technical Lead Name and Date:

Mark R. Seggel, Ph.D.
Acting CMC Lead (for DBRUP)
{*see electronic signature page*}

Table of Contents

Mark
Seggel

Digitally signed by Mark Seggel
Date: 8/21/2017 10:47:07AM
GUID: 507572b5000036176969356148025bae