

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205108Orig1s000**

**CHEMISTRY REVIEW(S)**

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Application:** NDA 205108/000  
**Code:** 110  
**Priority:** 3  
**Stamp Date:** 23-DEC-2013  
**PDUFA Date:** 23-OCT-2014  
**Action Goal:**  
**District Goal:** 24-AUG-2014

**Sponsor:** ARBOR PHARMS LLC  
 6 CONCOURSE PKY STE 1800  
 ATLANTA, GA 30328  
**Brand Name:** SOTALOL HYDROCHLORIDE  
**Estab. Name:**  
**Generic Name:** SOTALOL HYDROCHLORIDE  
**Product Number; Dosage Form; Ingredient; Strengths**  
 001; SOLUTION; SOTALOL; 5MG

<b>FDA Contacts:</b>	S. MCLAMORE	Prod Qual Reviewer	3017961710
	Y. KNIGHT	Product Quality PM	3017962133
	R. FORTNEY	Regulatory Project Mgr	3017961068
	K. SRINIVASACHAR	Team Leader	3017961760

<b>Overall Recommendation:</b>	ACCEPTABLE	on 29-JAN-2014	by C. CAPACCI-DANIEL ( )	3017963532
	PENDING	on 14-JAN-2014	by EES_PROD	
	PENDING	on 14-JAN-2014	by EES_PROD	

**Establishment:**      **CFN:** (b) (4)      **FEI:** (b) (4)  
 (b) (4)

**District:**      **AADA:**

**Responsibilities:**      DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE PACKAGER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER

**Profile:**      NON-STERILE API BY CHEMICAL SYNTHESIS      **OAI Status:**      NONE

**Last Milestone:**      OC RECOMMENDATION

**Milestone Date:**      15-JAN-2014

**Decision:**      ACCEPTABLE

**Reason:**      BASED ON PROFILE

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Profile:** NON-STERILE LIQUID (b) (4) OAI Status: NONE  
(b) (4)

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 15-JAN-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE OTHER TESTER

**Profile:** CONTROL TESTING LABORATORY OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 15-JAN-2014

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE OTHER TESTER

**Profile:** CONTROL TESTING LABORATORY OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 29-JAN-2014

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**NDA 205108****Sotalol Hydrochloride Oral Solution,  
5 mg/mL****Arbor Pharmaceuticals****Sherita D. McLamore-Hines, Ph.D.**Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment

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# Chemistry Review Data Sheet

1. NDA: 205108
2. REVIEW: #2
3. REVIEW DATE: September 26, 2014
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.

## 5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original Submission  
Amendment

December 23, 2013  
March 26, 2104

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Amendment

June 18, 2014

## 7. NAME & ADDRESS OF APPLICANT:

Name:

Arbor Pharmaceutical, LLC

Address:

980 Hammond Drive  
Suite 1250  
Atlanta, GA 30328

Telephone:

678-334-2420

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
- b) Non-Proprietary Name (USAN): Sotalol Hydrochloride
- c) Code Name/# (ONDC only): n/a
- d) Chem. Type/Submission
  - Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of life-threatening Ventricular Arrhythmias and Maintenance of Normal Sinus Rhythm in patients with history of highly symptomatic atrial fibrillation/Flutter

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 5 mg/mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

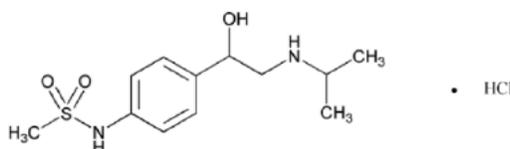
Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Methanesulphonamide, N-[-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-phenyl]-monohydrochloride

Molecular Formula:  $C_{12}H_{20}N_2O_3S \cdot HCl$

Molecular Weight: 308.82



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug Substance	1	Adequate	8/22/2014	N/A
	III	(b) (4)	(b) (4)	3	Adequate	10/5/2013	N/A
	III	(b) (4)	(b) (4)	3	Adequate	1/24/2012	N/A
	III	(b) (4)	(b) (4)	1	Adequate	5/27/2014	N/A
	III	(b) (4)	(b) (4)	4	Adequate	2/13/2012	N/A
	III	(b) (4)	(b) (4)	1	Adequate	5/27/2014	N/A
	III	(b) (4)	(b) (4)	1	Adequate	9/9/2014	
	III	(b) (4)	(b) (4)	1	Adequate	2/13/2012	N/A
	III	(b) (4)	(b) (4)	1	Adequate	8/14/2014	N/A
	III	(b) (4)	(b) (4)	3	Adequate	1/31/2012	N/A
	IV	(b) (4)	(b) (4)	1	Pending	9/8/2014	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

## Chemistry Review Data Sheet

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A	N/A	N/A
EES	Acceptable	1/2014	Sherita McLamore-Hines, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	No validation by FDA required	5/0120/14	Sherita McLamore-Hines, Ph.D.
DMETS	N/A	N/A	N/A
EA	Finding of no significant impact	6/19/2014	Sherita McLamore- Hines, Ph.D.
Microbiology	Acceptable	1/31/2014	Bryan Riley, Ph.D.

# The Chemistry Review for NDA 205108

## The Executive Summary

### A. Recommendation and Conclusion on Approvability

This application is recommended for approval from a CMC perspective.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC Phase 4 activity recommendations.

## II. Summary of Chemistry Assessments

Sotalol Hydrochloride is the active pharmaceutical ingredient in NDA 205-108. Sotalol Hydrochloride is manufactured by (b) (4). Sotalol Hydrochloride has a USP monograph and is an established active pharmaceutical ingredient that is currently approved as immediate release tablets (Betapace and Betapace AF) and in an intravenous formulation. Sotalol HCl drug substance is a non-hygroscopic, white to off-white powder with a molecular formula  $C_{12}H_{20}N_2O_3 \cdot S \cdot HCl$ , a molecular mass of 308.82 and a melting range of *ca.* 205-215°C. Sotalol Hydrochloride drug substance has been fully characterized. The applicant references DMF (b) (4) for a complete description of the manufacturing process and all relevant characterization data pertaining to (b) (4). DMF (b) (4) has been reviewed and is adequate to support this application.

The drug product is Sotalol Hydrochloride Oral Solution. Betapace was approved under NDA 19-865 in 1992. Betapace AF was approved under NDA 21-151 in 2000. Betapace is indicated for the treatment of life-threatening Ventricular Arrhythmias. Betapace AF is indicated for the maintenance of Normal Sinus Rhythm in patients with history of highly symptomatic atrial fibrillation/Flutter. The drug product, Sotalol Hydrochloride Oral Solution is being developed for both (the treatment of life-threatening Ventricular Arrhythmias and Maintenance of Normal Sinus Rhythm in patients with history of highly symptomatic atrial fibrillation/Flutter). It is being developed for patients who are unable to swallow tablets or who require naso-gastric tube administration

The drug product is presented as a 5 mg/ml oral solution containing Sotalol Hydrochloride USP (b) (4), purified water (b) (4), citric acid (b) (4), (b) (4), sodium citrate (b) (4), sucralose (b) (4), sodium benzoate (b) (4), and grape flavor (b) (4). The drug product manufactured by (b) (4) with a typical commercial batch size of (b) (4). The drug product will be packaged in two packaging configurations: 250 mL and (b) (4) mL (b) (4) bottle with an induction seal and a (b) (4) cap. The applicant provided detailed descriptions of each packaging component and referenced the appropriate DMFs for a more comprehensive description.

## Executive Summary Section

The applicant has requested a 15 month expiry for the drug product. Twelve months of long term (25°C/60%RH) and intermediate (30°C/65%RH) stability data and 6 months accelerated (40°C/75%RH) stability data was presented for three registration drug product batches (batches MFYN, MFYP and MFYS). The registration batches were manufactured at (b)(4) and were each packaged into the intended 250 mL and 480 mL bottle commercial container closure systems. There were no stability trends observed and all data were comparable and within the prescribed specifications. As such, the applicant has provided adequate data to support the requested 15 month and the 15 month expiry is granted.

**B. Description of How the Drug Product is Intended to be Used**

The recommended dosing regimen includes a starting dose of 80 mg administered twice daily up to a maximum daily dose of 640 mg (320 mg twice daily).

The proposed commercial container closure system for Sotalol Oral Solution 5 mg/mL are 250 (b)(4) round amber bottles with (b)(4) induction seal caps and (b)(4) round amber bottles with (b)(4) induction seal caps.

**C. Basis for Approvability or Not-Approval Recommendation**

From a CMC perspective, this application is recommended for approval as the applicant has adequately responded to all concerns outlined in review #1 as well as subsequent comments that resulted from later amendments. The drug substance was determined to be safe, effective, and manufactured in a consistent manner with inherent quality in DMF (b)(4). The sponsor identified CQA and established controls to ensure the quality of the drug product. The results of the batch analyses confirm quality of the drug product at release. The intended commercial packaging presentations provide adequate protection of the drug product and ensure drug product quality over the proposed 15-month shelf-life as demonstrated through the drug product stability data. Additionally, the draft bottle labels and package insert are acceptable from a CMC perspective.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

SMcLamore-Hines  
OStephens

**C. CC Block**

Orig. NDA 205108

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/s/  
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SHERITA D MCLAMORE  
09/26/2014

OLEN M STEPHENS  
09/26/2014

**NDA 205108****Sotalol Hydrochloride Oral Solution,  
5 mg/mL****Arbor Pharmaceuticals****Sherita D. McLamore-Hines, Ph.D.**Division of Pre-Marketing Assessment 1  
Office of New Drug Quality Assessment

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# Chemistry Review Data Sheet

1. NDA: 205108
2. REVIEW: #1
3. REVIEW DATE: June 19, 2014
4. REVIEWER: Sherita D. McLamore-Hines, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

n/a

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission  
Amendment

Document Date

December 23, 2013  
March 26, 2104

7. NAME & ADDRESS OF APPLICANT:

Name:

Arbor Pharmaceutical, LLC

Address:

980 Hammond Drive  
Suite 1250  
Atlanta, GA 30328

Telephone:

678-334-2420

8. DRUG PRODUCT NAME/CODE/TYPE:

## Chemistry Review Data Sheet

- a) Proprietary Name: Pending  
 b) Non-Proprietary Name (USAN): Sotalol Hydrochloride  
 c) Code Name/# (ONDC only): n/a  
 d) Chem. Type/Submission
- Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of life-threatening Ventricular Arrhythmias and Maintenance of Normal Sinus Rhythm in patients with history of highly symptomatic atrial fibrillation/Flutter

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 5 mg/mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

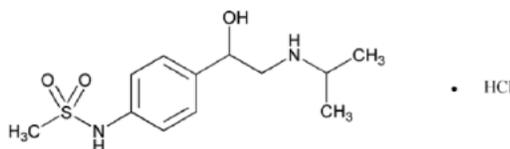
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Methanesulphonamide, N-[-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-phenyl]-monohydrochloride

Molecular Formula: C<sub>12</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>S · HCl

Molecular Weight: 308.82



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug Substance	1	Adequate	12/06/2012	N/A
	III	(b) (4)	(b) (4)	3	Adequate	10/5/2013	N/A
	III	(b) (4)	(b) (4)	3	Adequate	1/24/2012	N/A
	III	(b) (4)	(b) (4)	1	Adequate	5/27/2014	N/A
	III	(b) (4)	(b) (4)	4	Adequate	2/13/2012	N/A
	III	(b) (4)	(b) (4)	1	Adequate	5/27/2014	N/A
	III	(b) (4)	(b) (4)	1	Pending		N/A
	III	(b) (4)	(b) (4)	1	Adequate	2/13/2012	N/A
	III	(b) (4)	(b) (4)	1	Pending		N/A
	III	(b) (4)	(b) (4)	3	Adequate	1/31/2012	
	IV	(b) (4)	(b) (4)	1	Pending		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

## Chemistry Review Data Sheet

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A	N/A	N/A
EES	Acceptable	1/2014	Sherita McLamore-Hines, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	No validation by FDA required	5/0120/14	Sherita McLamore-Hines, Ph.D.
DMETS	N/A	N/A	N/A
EA	Finding of no significant impact	6/19/2014	Sherita McLamore- Hines, Ph.D.
Microbiology	Acceptable	1/31/2014	Bryan Riley, Ph.D.

# The Chemistry Review for NDA 205108

## The Executive Summary

### A. Recommendation and Conclusion on Approvability

At this time a recommendation for the Chemistry, Manufacturing, and Controls (CMC) section of NDA 205108 is pending. The approval from a CMC standpoint is contingent on an acceptable response to the CMC deficiencies outlined below:

1. *Propose an acceptance criterion for the specific gravity in-process test*
2. *The in-house specification for the grape flavor does not include a test and acceptance criterion for identity. Update the specification for the grape flavor to include a test for identification.*
3. *Specify an upper limit for the filling volume in-process control.*
4. *Confirm that the re-validation of method CTMLP-3056 will include related substance (b) (4)*
5. *The proposed acceptance criterion for specific gravity and (b) (4) in the drug product specification is "report results". Propose acceptance criteria based on available data or provide justification for the exclusion.*
6. *Update the stability protocol for the first three commercial batches to include testing on the upright bottle configuration or provide justification for the exclusion of this orientation.*
7. *Confirm that your routine stability program includes testing for the inverted and upright bottle configurations*
8. *Your stability protocol included reduced testing at T=9 months and you indicate that "matrixing may be performed for pull points post the expiration date". While the agency has accepted the stability data with the reduced testing at T=9 months without a prior agreement, future bracketing or matrixing strategies should be agreed upon with the Agency prior to implementing that stability protocol change.*
9. *Revise the drug product stability protocol to include testing for related substance (b) (4)*
10. *Provide a stability update for the 12 month time point.*
11. *Submit your Methods Validation Package*
12. *The Description section of the package insert includes the following statement "Each 5 mL contains 5 mg Sotalol HCl". As the drug product is formulated as a 5 mg/mL, all labeling should be updated reflect this concentration.*

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

Sotalol Hydrochloride is the active pharmaceutical ingredient in NDA 205-108. Sotalol Hydrochloride is manufactured by (b) (4). Sotalol Hydrochloride has a USP monograph and is an established active pharmaceutical ingredient that is currently approved as immediate release tablets

## Executive Summary Section

(Betapace and Betapace AF) and in an intravenous formulation. Sotalol HCl drug substance is a non-hygroscopic, white to off-white powder with a molecular formula  $C_{12}H_{20}N_2O_3 \cdot S \cdot HCl$ , a molecular mass of 308.82 and a melting range of *ca.* 205-215°C. Sotalol Hydrochloride drug substance has been fully characterized. The applicant references DMF (b) (4) for a complete description of the manufacturing process and all relevant characterization data pertaining to (b) (4). DMF (b) (4) has been reviewed and is adequate to support this application.

The drug product is Sotalol Hydrochloride Oral Solution. Betapace was approved under NDA 19-865 in 1992. Betapace AF was approved under NDA 21-151 in 2000. Betapace is indicated for the treatment of life-threatening Ventricular Arrhythmias. Betapace AF is indicated for the maintenance of Normal Sinus Rhythm in patients with history of highly symptomatic atrial fibrillation/Flutter. The drug product, Sotalol Hydrochloride Oral Solution is being developed for both (the treatment of life-threatening Ventricular Arrhythmias and Maintenance of Normal Sinus Rhythm in patients with history of highly symptomatic atrial fibrillation/Flutter). It is being developed for patients who are unable to swallow tablets or who require naso-gastric tube administration

The drug product is presented as a 5 mg/ml oral solution containing Sotalol Hydrochloride USP (b) (4), purified water (b) (4), citric acid (b) (4), (b) (4), sodium citrate (b) (4), sodium benzoate (b) (4), and grape flavor (b) (4). The drug product manufactured by (b) (4) with a typical commercial batch size of (b) (4). The drug product will be packaged in two packaging configurations: 250 mL and (b) (4) mL (b) (4) bottle with an induction seal and a (b) (4) cap. The applicant provided detailed descriptions of each packaging component and referenced the appropriate DMFs for a more comprehensive description.

The applicant has not requested an expiry for the drug product. Eleven months of long term (25°C/60%RH) and intermediate (30°C/65%RH) stability data and 6 months accelerated (40°C/75%RH) stability data was presented for three registration drug product batches (batches MFYN, MFYP and MFYS). The registration batches were manufactured at (b) (4) and were each packaged into the intended 250 mL and 480 mL bottle commercial container closure systems. While there were no stability trends observed and all data were comparable and within the prescribed specifications, the applicant has not provided adequate data to support any expiry for the drug product. A shelf-life recommendation will be made after the applicant has provided the most recent stability update.

**B. Description of How the Drug Product is Intended to be Used**

The recommended dosing regimen includes a starting dose of 80 mg administered twice daily up to a maximum daily dose of 640 mg (320 mg twice daily).

## Executive Summary Section

The proposed commercial container closure system for Sotalol Oral Solution 5 mg/mL are 250 (b) (4) round amber bottles with (b) (4) induction seal caps and (b) (4) round amber bottles with (b) (4) induction seal caps.

**C. Basis for Approvability or Not-Approval Recommendation**

A recommendation for the approvability of NDA 204308 from a CMC perspective cannot be determined until the concerns related to the manufacture and control of the drug product as outlined in this review have been adequately addressed.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

SMcLamore-Hines

OStephens

**C. CC Block**

Orig. NDA 205108

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/s/  
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SHERITA D MCLAMORE  
06/23/2014

OLEN M STEPHENS  
06/23/2014

# Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

## I. Review Cover Sheet

- 1. OMPQ Reviewer: Vibhakar Shah, Ph.D.
- 2. NDA/BLA Number: 205108
  - Submission Date: 12/23/2013
  - 21<sup>st</sup> C. Review Goal Date: 09/18/2014
  - PDUFA Goal Date: 10/23/2014

### 3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Sotylize (proposed)
Established or Non-Proprietary Name (USAN) and strength:	Sotalol hydrochloride
Dosage Form:	Oral Solution

### 4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Arbor Pharmaceuticals, LLC
Responsible Organization (OND Division):	Division of Cardio-Renal Drug Products

## II. Application Detail

1. INDICATION: Treatment of documented life-threatening ventricular arrhythmias and for the maintenance of normal sinus rhythm in patients with history of highly symptomatic atrial fibrillation/flutter
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 5 mg/mL
4. Rx/OTC DISPENSED:  Rx  OTC
5. ELECTRONIC SUBMISSION (yes/no)?  Yes  No
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		DMF <sup>(b) (4)</sup> is referenced for the drug substance
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug	-	-	-	Not applicable
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		Not applicable/relevant at this stage.
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

### III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		All sites involved in the manufacture of drug substance and product are stated to be ready on the form 356h.
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	X		
			X	
			X	

\*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review  
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<b>IMA CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
17.	Does this application fit one of the EES Product Specific Categories?		X	<ul style="list-style-type: none"> <li>- NME</li> <li>- 1<sup>st</sup> Generic</li> <li>- 1<sup>st</sup> FDA evaluation for the establishment</li> <li>- 1<sup>st</sup> application for the sponsor</li> <li>- Narrow therapeutic</li> <li>- New dosage form for the establishment</li> <li>- High risk API process</li> <li>- New complex Mfg elements (QbD/PAT/RTRt)</li> <li>- New product fill line</li> <li>- Newly constructed Mfg area</li> <li>- Facility becoming multi-product</li> <li>- Potent product</li> </ul>
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		Based on prior GMP inspectional history for the respective profile codes no PAI has been deemed necessary for all NDA listed establishments. All facilities have been deemed acceptable.
19.	<b>From a CGMP/facilities perspective, is the application fileable?</b>  If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

## IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			NO
<input type="checkbox"/>	RTRT Proposal	PAT	Drug/Device Combo
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PET	Design Space	Continuous Mfg	Naturally derived API
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (explain):			

### Manufacturing Highlights:

#### 1. Drug Substance

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

#### 2. Drug Product

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

#### 3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)

The facilities listed for the manufacture of the DS as well as the DP are all foreign sites (see Establishment Evaluation Status table on page 8)

**Additional information on Manufacturing issues or Complexities**

**Drug Substance:**

Manufacture of *drug substance* is referred to DMF

(b) (4)

Sotalol hydrochloride.

(b) (4)

**Drug Product:** This is a 505(b)(2) application for a new dosage form, *oral solution* of sotalol hydrochloride. Sotalol has been previously approved as sotalol *tablet* for the same indication under two NDAs: NDA 19865 for Betapace tablet and NDA 21151 for Betapace AF tablet.

(b) (4) is the manufacturer of the drug product Sotalol Oral solution. The manufacturing process is straightforward and involves: (b) (4)

(b) (4)

(b) (4)

## Drug substance and Drug Product Manufacturing Facilities Chart



**AC:** Acceptable; **NA:** Not Applicable; **TBD:** To be determined; **PN:** Pending

## V. Overall Conclusions and Recommendations

<b>Is the application fileable? (yes/no)</b>	<b>YES</b>
<b>At this time, is a KTM warranted for any PAI? (yes – site / no):</b>	<b>YES</b>
<b>Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no):</b>	<b>NO</b>
Comments for 74 Day Letter	<b>None</b>
1.	
2.	
3.	

## REVIEW AND APPROVAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

VIBHAKAR J SHAH  
03/19/2014

MAHESH R RAMANADHAM  
03/19/2014

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**IQA and Filing Review Cover Sheet**

1. NEW DRUG APPLICATION NUMBER: 205108

2. DATES AND GOALS:

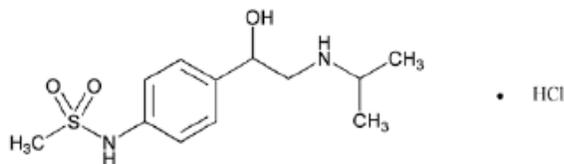
Letter Date: Dec. 23, 2013	Submission Received Date : Dec. 23, 2013
PDUFA Goal Date:	Oct. 23, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Sotylize (proposed)
Established or Non-Proprietary Name (USAN):	Sotalol hydrochloride
Dosage Form:	Oral solution
Route of Administration	Oral
Strength/Potency	5 mg/mL
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of documented life-threatening ventricular arrhythmias and for the maintenance of normal sinus rhythm in patients with history of highly symptomatic atrial fibrillation/flutter

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h):

Arbor Pharmaceuticals, LLC

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**7. SUBMISSION PROPERTIES:**

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 3
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Cardiovascular and Renal Products

**8. CONSULTS:**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology

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## **Overall Filing Conclusions and Recommendations**

### **CMC:**

**Is the Product Quality Section of the application fileable from a CMC perspective?**

Yes

**Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?**

Yes

**CMC Comments for 74-Day Letter:**

1. Methods Validation Package is missing and should be submitted in Section 3.2.R

### **Microbiology:**

**Is the Product Quality Section of the application fileable from a Microbiology perspective?**

Yes

**Microbiology Filing Issues:** None. See email below

From: CDER OPS IO MICRO

Sent: Thursday, January 16, 2014 2:08 PM

To: Srinivasachar, Kasturi; CDER OPS IO MICRO

Subject: RE: Successfully Processed ECTD: NDA205108 in DARRTS.

This submission is acceptable from a product quality microbiology standpoint and will be recommended for approval. Therefore, no product quality microbiology reviewer assignment will be made for this submission. A review memo describing the assessment of the microbial controls for the drug product will be entered into DARRTS.

Thanks, Vera

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Summary of Initial Quality Assessment**

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	

Is a team review recommended?	No
Suggested expertise for team: No special expertise required. Drug substance information in DMF (b)(4) has been previously reviewed. Simple formulation and manufacturing process.	

**Summary of Critical Issues and Complexities**

Drug Substance:

- The response to the deficiency sent to the DMF holder should be evaluated and any subsequent amendments reviewed.
- (b)(4)
- The Applicant has proposed (b)(4) limits for individual impurities than USP but has maintained the USP acceptance criterion for total impurities. The same is true for the limit of (b)(4). Is this acceptable?

Drug Product:

- A large number of DMF references for various packaging components and the non-compensial excipient, grape flavor have been submitted. All these DMFs have multiple listings and only the ones specified should be evaluated. For example, (b)(4) has a number of grape flavors listed and some of these have been previously reviewed; however, for this application the LoA specifies (b)(4) and this should be reviewed.
- Executed batch records for the registration batches have been submitted for this 505(b)(2) application but there is no Master Batch Record as required under 314.54 (a)(1)(i).
- Regarding the product specification –
  - Should Deliverable Volume (USP <698>) be included?
  - Is the proposed acceptance criterion of (b)(4)% for sodium benzoate justified?
  - A test for extractables is not listed. Do the data submitted justify this omission?
  - Is a total of NMT (b)(4)% for related substances/degradants acceptable given the low level of individual degradation products?
  - It should be noted that USP has assay limits of 95-105% for sotalol *tablets*.
- Regarding Stability –
  - At least 12 months' long term data are needed to assign an expiration date. The Applicant should be requested to submit these as soon as possible.
  - Matrixing has been proposed for the registration batch stability protocol "in communication with the Agency". However, this is not reflected in the meeting

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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minutes or other correspondence. Does this matter? The protocol for the first 3 commercial batches includes only the inverted configuration of the bottles. Is this acceptable?

- It is stated that the (b)(4) bottle (b)(4) will be used for registration batches and commercially until exhausted followed by the use of (b)(4) bottles. Are these (b)(4) equivalent in their protective properties? Will the bottles made from the new (b)(4) be used in the stability studies on the first 3 commercial batches?
- A Methods Validation Package has not been submitted in section 3.2.R
- Regarding Labeling—
  - The nonproprietary name is based on the hydrochloride salt rather than the active moiety contrary to the USP salt nomenclature policy. The strength of 5 mg/mL is based on the salt. Does this qualify as an exception to the policy given that an approved dosage form (tablets) of this drug is also named as the hydrochloride salt?
  - There are glaring errors in the draft PI section 11 (Description) – structure of sotalol, strength (“each 5 mL contains 5 mg..”) which need correction.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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## Initial Quality Assessment

This is a 505(b)(2) application for a new dosage form, oral solution, of sotalol hydrochloride. Sotalol has previously been approved for the same indication as Betapace and Betapace AF tablets (NDAs 19-865 and 21-151). The Applicant relies entirely on FDA's findings of safety and efficacy for the Betapace NDAs so there are no pre-clinical or clinical data in the NDA. A request for waiver of in-vivo bioavailability (BA/BE) studies has been submitted. Only one meeting has been held with the Applicant prior to NDA submission and no CMC issues were discussed at this meeting. However, in the stability section it is stated that "a stability matrix was generated for the registration batches in communication with the Agency". This is not reflected in the official meeting minutes.

**Drug Substance:** Sotalol hydrochloride is a white or almost white powder with melting point 205-215 °C. It is freely soluble in water, soluble in alcohol and practically insoluble in methylene chloride. A flow diagram for the (b) (4) DMF (b) (4) is given for details. The specification for the drug substance in the NDA is essentially based on the USP monograph with an additional test for (b) (4) impurity limits. Data are provided for three batches of drug substance used in the manufacture of drug product registration/stability batches. The batch sizes are (b) (4). No retest period is mentioned in the NDA; presumably, this is stated in the DMF in conjunction with the stability data.

**Drug Product:** Sotalol hydrochloride oral solution is a clear, colorless liquid containing 5 mg/mL of sotalol hydrochloride. The excipients used are typical for this type of dosage form – citric acid and sodium citrate (b) (4), sodium benzoate, a (b) (4) sucralose, (b) (4) and grape flavor. With the exception of grape flavor, all are compendial grade. All excipients are within the IIG limits for an oral route of administration. The product is packaged in 2 configurations-- 250 mL in a 250 mL amber (b) (4) bottle with a (b) (4) cap with an induction seal and 480 mL (b) (4) bottle with (b) (4) cap and induction seal.

The formulation development has been described in detail including initial work at (b) (4) and at the proposed commercial site, (b) (4). The 5 mg/mL concentration was chosen to match the RLD's marketed strength. A citric acid/sodium citrate buffer system was chosen to achieve a pH of 5 since it was known from the literature that this was optimal for sotalol hydrochloride stability. (b) (4) In order to keep the osmolality of the finished product below 400mOsm/kg, limited use of (b) (4) was indicated. Initial formulations manufactured contained (b) (4) sodium benzoate. The former necessitated the use of (b) (4), which increased the osmolality of the solution. A formulation using sodium benzoate was selected for further development and scale-up at (b) (4), the proposed commercial production site. Scale – up to registration batch size of (b) (4) was achieved by adjusting citrate buffer concentration to give a final pH (b) (4).

It was established that a storage time of (b) (4) for the bulk solution had no negative impact on chemical or microbial quality. The Applicant concludes that the data from the

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registration batches support scale-up to the proposed commercial batch size of (b) (4)

The manufacturing process is (b) (4)

Product specifications include the customary test attributes for an oral solution -- appearance, identification, assay for sotalol hydrochloride, assay for sodium benzoate, pH, and microbial limits. Specific gravity and osmolality are also tested. Batch analysis of 3 registration batches tested to these specifications have been submitted. Stability data have been generated on these registration batches and 8 months' data at 25 °C/60% RH and 30 °C/65% RH as well as 6 months' data at 40 °C/75% RH are available. Photostability has been carried out on 1 registration batch packaged in both 250 mL and 480 mL configurations in accordance with ICH Q1B. The Applicant states that an expiration date will be proposed after additional stability data are available.

**Additional Comments:** Facilities for inspection have been entered in the EES database and an Overall Recommendation of "Acceptable" has already been given (Jan 29, 2014). Methods validation will not be requested at this time since this is not an NME. Categorical exclusion from environmental assessment has been requested based on 21CFR 25.31(b). The Biopharmaceutics Overall Filing Conclusions and Recommendations and the Biopharmaceutics Filing Checklist have been removed from this IQA /Filing Review because, by mutual agreement these will be separately filed in DARRTS for this NDA.

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## FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			NA

B. FACILITIES*				
<b>* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.</b>				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

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	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

**C. ENVIRONMENTAL ASSESMENT**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Cross-reference to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?			Cross-reference to DMF (b) (4)
15.	Does the section contain controls for the DS?			Cross-reference to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?			Cross-reference to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		No master batch record
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			NA
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		No expiration date proposed
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?		X	

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<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		See table below

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	II	Moehs Iberica S.L.		6-25-2013	
	IV			9-6-2013	
	III			11-25-2013	
	III			11-22-2013	
	III			7-3-2013 and 8-18-2013	
	III			11-22-2013	
	III			9-11-2013	
	III			12-12-2013 12-18-2013	
	III			8-27-2013	
	III			12-12-2013	
	III			11-22-2013	

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<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

*See appended electronic signature page*

*Kasturi Srinivasachar, Ph.D*

CMC-Lead or

Division I, Branch 1

Office of New Drug Quality Assessment

*See appended electronic signature page*

*Olen Stephens, Ph.D.*

Acting Branch Chief

Division I, Branch 1

Office of New Drug Quality Assessment

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KASTURI SRINIVASACHAR  
02/12/2014

OLEN M STEPHENS  
02/12/2014