

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205108Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 205-108	Reviewer:	
Division:	DCRP	Sandra Suarez Sharp, Ph.D.	
Applicant:	Arbor Pharmaceuticals, LLC	Team Leader:	
Trade Name:	Sotylize Oral Solution	Angelica Dorantes, Ph.D.	
Generic Name:	Sotalol hydrochloride Oral Solution, 5 mg/mL	Date Assigned:	Jan 01, 2014
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	Date of Review:	Sep 12, 2014
Formulation/strength	Oral Solution, 5 mg/mL		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission dates		Date of informal/Formal Consult	PRIMARY REVIEW DUE DATE
Dec 23, 2013		Jan 01, 2013	Sep 16, 2014
Type of Submission:	505(b)(2)		
Type of Consult:	Biowaiver Request		
SUMMARY OF BIOPHARMACEUTICS FINDINGS			
Background:			
<p>The proposed drug product, Sotylize Oral Solution, contains the active ingredient sotalol hydrochloride USP, a pharmacological agent known as a beta-adrenergic blocking agent. This 505 (b)(2) submission makes reference to the compounded syrups of two FDA approved products, 1) Betapace Syrup 5 mg/mL compounded from Betapace 120 mg tablets (NDA 19-865), and; 2) Betapace AF Syrup 5 mg/mL compounded from Betapace AF 120 mg tablets (NDA 21-151). Sotalol is considered a highly soluble drug substance. The oral BA of sotalol following administration of the tablets was 90-100%. Betapace tablets are rapidly dissolving (e.g. (b)(4)% in 15 min.</p>			
Submission:			
<p>In accordance to 21 CFR 320.22 (b) (3), the Applicant is requesting a waiver of the required BA/BE studies for their proposed Sotalol oral solution.</p>			

The data submitted to support the biowaiver are summarized below:

1. The proposed drug product is an oral solution
2. Contains an active ingredient (s) in the same concentration and dosage form as an FDA-approved reference product
3. Contains no inactive ingredients or change in formulation that may significantly affect absorption of the active ingredient

Review:

This review summarizes and makes recommendations in terms of the acceptability of the biowaiver request.

Reviewer's Assessment:

1. The drug product contains an active ingredient (s) in the same concentration and dosage form as an FDA-approved reference product

Side-by-side table comparison of the chemical components and composition of the proposed product and the listed drugs provided evidence of same concentration. Evidence of same dosage form was supported by:

- Betapace and Betapace AF labeling statement for the compounding syrup: *“This compounding procedure results in a solution containing 5 mg/mL of sotalol HCl. The fine solid particles are the water-insoluble inactive ingredients of the tablets.”* and;
- The Applicant prepared an extemporaneous suspension (in triplicate) according to the label instructions. For all tested samples the concentration ranged from 4.96-5.03 mg/mL) indication the presence of a true solution.

2. The drug product contains no inactive ingredients or change in formulation that may significantly affect absorption of the active ingredient

The proposed product contains no known inactive ingredients affecting the BA of the proposed product. In addition, the osmolarity of the proposed solution (212 mOsm/Kg) is within the range of the osmolarity of the marketed tablet in deionized water (39 mOsm/Kg) and the osmolarity of the extemporaneously prepared solution (2860 mOsm/Kg). Furthermore, the pH for Sotalol HCl Solution (pH 5.1) falls within the range of the pH for the marketed Sotalol Hydrochloride Tablet in deionized water (pH 5.4) and the pH (pH 2.4) of the extemporaneously prepared solution.

The Betapace Tablets dissolved (^{(b)(4)}%) in less than 10 min using 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, paddle, 50 rpm. All tablets were completely disintegrated within 5 in for all media tested.

It should be noted that the Applicant's proposed product does not fully satisfy the criteria for granting a waiver of evidence of in vivo bioavailability under 21 CFR 320.22 (a), (b). Specifically, the Applicant cannot cite reliance on the compounded syrup described in the Betapace and Betapace AF labeling, because the compounded syrup is not a listed drug; however, based 21 CFR 320.24(b)(6), the Applicant can rely on information about the compounded syrup in Betapace's and Betapace AF's approved labeling to the extent that the clinical division (DCaRP) finds it scientifically adequate.

Therefore, Biopharmaceutics considers that the BA/BE waiver request for this NDA is adequately supported by the following data:

- Sotalol is considered a highly soluble and permeable drug substance.
- The oral bioavailability of sotalol following administration of the tablets was 90-100%.
- Betapace tablets are rapidly dissolving (e.g. (b)(4)% in 15 min.
- Under these circumstances, it can be assumed that the bioavailability of sotalol administered as a solution is very similar to that following the tablet administration and therefore these products are bioequivalent.

Risk Assessment Evaluation:

Refer to the CMC review for the quality risk assessment table of this product. Given that the drug substance is highly soluble and the drug product is an stable solution for oral administration with high bioavailability, from the Biopharmaceutics perspective, Sotylize Oral Solution is considered a low risk drug product.

RECOMMENDATION:

ONDQA-Biopharmaceutics had reviewed NDA 205-108 submitted on December 23, 2013. The provided data support the acceptability of the BA/BE waiver request and the biowaiver is GRANTED.

From the Biopharmaceutics perspective, Sotylize (sotalol hydrochloride) Oral Solution 5 mg/mL under NDA 205-108 is recommended for **APPROVAL**.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

cc : PSeo

BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

The proposed drug product, Sotylize Oral Solution, contains the active ingredient sotalol hydrochloride USP, a pharmacological agent known as a beta-adrenergic blocking agent. This 505 (b)(2) submission makes reference to the compounded syrups of two FDA approved products, 1) Betapace Syrup 5 mg/mL compounded from Betapace 120 mg tablets (NDA 19-865). Betapace tablets 80 mg, 120 mg, 160 mg, 240 mg, and 320 mg approved by FDA on Oct 1992. Betapace is indicated for the treatment of documented ventricular arrhythmias; and 2) Betapace AF Syrup 5 mg/mL compounded from Betapace AF 120 mg tablets (NDA 21-151). Betapace AF tablets 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 160 mg approved by FDA on Feb 2000. Betapace AF is indicated for the maintenance of normal sinus in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. Sotalol is considered a highly soluble. The oral BA of sotalol following administration of the tablets was 90-100%. Betapace tablets are rapidly dissolving (e.g. > ^(b)₍₄₎% in 15 min.

This review summarizes and makes recommendations in terms of the acceptability of the biowaiver request for the proposed product, Sotalol Hydrochloride Oral Solution, 5 mg/mL.

CHEMISTRY

Drug Substance

Some key general properties for the drug substance are summarized in the table below.

Property	Result
Appearance	White or almost white powder
Solubility	Freely soluble in water, soluble in alcohol, and practically insoluble in methylene chloride
Melting range	205°C-215 °C

Drug Product

Sotalol Hydrochloride Oral Solution is a clear, colorless liquid containing 5 mg/mL of sotalol hydrochloride. The manufacturing process for Sotalol Hydrochloride Oral Solution is defined as the mixing of both powder and liquid components into a homogeneous solution.

The quantitative composition and the IIG levels for Sotalol Hydrochloride Oral Solution are described in Table 1. Sotalol Hydrochloride Oral Solution is packaged as a 250 mL product in a 250 mL round, amber ^(b)₍₄₎ bottle with a 24 mm

white (b) (4) cap with an induction seal. Sotalol Hydrochloride Oral Solution may also be packaged as a 480 mL product in a (b) (4) mL round, amber (b) (4) bottle with a 28 mm white (b) (4) cap with an induction seal.

Table 1. Quantitative Composition for Sotalol Hydrochloride Oral Solution

Ingredients	Function	Quality Standard	% Volume (w/w)	IIG Level
Sotalol hydrochloride	Active	USP	0.500	N/A
(b) (4)	(b) (4)	USP	(b) (4)	(b) (4)
Citric acid (b) (4)		USP		
Sodium citrate (b) (4)		USP		
Sucralose		NF		
Sodium benzoate		NF		
Grape flavor		In-house		
Purified water		USP		

DATA SUPPORTING THE BIOWAIVER REQUEST

In accordance to 21 CFR 320.22 (b) (3), the Applicant requested a biowaiver of the required BA/BE studies for their proposed Sotalol HCl oral solution. The data submitted to support the biowaiver are summarized as follows:

- The proposed drug product is an oral solution
- Contains an active ingredient (s) in the same concentration and dosage form as an FDA-approved reference product
- Contains no inactive ingredients or change in formulation that may significantly affect absorption of the active ingredient

The active ingredient, Sotalol HCl and all inactive ingredients in the Arbor Solution formulation are all well within their respective water solubilities shown in Table 2, indicating that all active and inactive ingredients are in solution in this product.

Table 2. Active and inactive ingredients water solubilities

Component	Quality Standard	Water Solubility ¹
Sotalol HCl	USP	(b) (4)
Sodium citrate (b) (4)	USP	(b) (4)
Citric acid (b) (4)	USP	(b) (4)
Sucralose	NF	(b) (4)
Sodium benzoate	NF	(b) (4)
Grape flavor ¹	In-house	(b) (4)
Purified water	USP	(b) (4)

¹Data from (b) (4) Database, water solubilities
At room temperature

Contains an active ingredient (s) in the same concentration and dosage form as an FDA-approved reference product

A side by side table comparison of the chemical components and composition of the proposed product and the listed drugs is provided in the table below. The FDA-approved extemporaneous Oral Solution and Arbor’s Sotalol Oral Solution are both aqueous solution of sotalol HCl and both contain sotalol HCl at the same concentration, 5 mg/mL.

Arbor (Potential Formulations) [‡]		Betapace/Betapace AF	
Sotalol HCL Oral Solution (Sodium Benzoate as (b) (4))	Sotalol HCL Oral Solution (b) (4)	Extemporaneous Oral Solution	Oral Tablet
Sotalol HCl – 0.5%	(b) (4)	5 mg/mL Betapace	120 mg sotalol HCL/tablet [†]
(b) (4) Citrate (b) (4)	(b) (4)	Microcrystalline cellulose	Microcrystalline cellulose
Citric Acid – (b) (4)	(b) (4)	Lactose	Lactose
Sucralose – (b) (4)	(b) (4)	Starch	Starch
-	(b) (4)	Stearic Acid	Stearic Acid
-	(b) (4)	Magnesium Stearate	Magnesium Stearate
-	(b) (4)	Colloidal silicon dioxide	Colloidal silicon dioxide
Grape Flavor – (b) (4)	(b) (4)		(b) (4)
Purified Water	(b) (4)		(b) (4)
Sodium Benzoate – (b) (4)	(b) (4)		(b) (4)
-	(b) (4)		(b) (4)
-	(b) (4)		(b) (4)

Evidence of same dosage form was supported by the following information:

- Betapace and Betapace AF labeling¹ statement for the compounding syrup: “*This compounding procedure results in a solution containing 5 mg/mL of sotalol HCl. The fine solid particles are the water-insoluble inactive ingredients of the tablets.*” and;
- The Applicant prepared an extemporaneous suspension (in triplicate) according to the label instructions. For all tested samples the concentration ranged from 4.96-5.03 mg/mL) indication the presence of a true solution.

Contains no inactive ingredients or change in formulation that may significantly affect absorption of the active ingredient

The proposed product contains no known inactive ingredients affecting the BA of the proposed product. In addition, the osmolality of the proposed solution (212 mOsm/Kg) is within the range of the osmolality of the marketed tablet in deionized water (39 mOsm/Kg) and the osmolality of the extemporaneously prepared solution (2860 mOsm/Kg) (Table 3). Furthermore, the pH for Sotalol HCl Solution (pH 5.1) falls within range of the pH for the marketed Sotalol Hydrochloride Tablet in deionized water (pH 5.4) and the pH of the extemporaneously prepared solution (pH 2.4).

Table 3. Comparative pH and Osmolality of Arbor’s Prototype Sotalol HCl Oral Solution, Sotalol Extemporaneous Oral Solution, and Sotalol HCl Tablets in Water

Undiluted Sample	pH	Osmolality(mOsm/kg)
Sotalol HCl Tablets in Deionized Water	5.4	39
Arbor’s Sotalol HCl Oral Solution	5.1	212
Sotalol <i>Extemporaneous Oral Solution</i>	2.4	2860

In addition, as suggested by the FDA during the pre-NDA meeting the Applicant performed tablet dissolution and disintegration studies on the marketed Bayer Sotalol HCl 120 mg tablets to determine if there might be a significant lag in absorption. The Betapace Tablets dissolved ^{(b)(4)}%) in less than 10 min using 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, paddle, 50 rpm. All tablets were completely disintegrated within 5 in for all media tested. These data indicate rapid dissolution and therefore, no potential lag time in absorption (e.g. same Tmax for the tablet vs. solution).

It should be noted that the 505(b)(2) Applicant’s proposed product does not appear to satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR 320.22 (a), (b). Specifically, the Applicant cannot cite reliance on the compounded syrup described in the Betapace and Betapace AF labeling, because the compounded syrup is not a listed drug; however, based 21 CFR 320.24(b)(6), the Applicant can rely on information about the compounded syrup in Betapace’s and Betapace AF’s approved labeling to the extent that the review team finds it scientifically relevant.

¹ Drugs at the FDA

Therefore, from the biopharmaceutics perspective, the biowaiver request for this NDA is supported by the following data:

- Sotalol is considered a highly soluble drug substance².
- The oral BA of sotalol following administration of the tablets was 90-100%³.
- Betapace tablets are rapidly dissolving (e.g. (b) (4)% in 15 min).
- Under these circumstances one can assume that the PK of sotalol administered as a solution will be very similar to that following the tablet administration.

The provided data supporting the biowaiver request are acceptable and the BA/BE waiver is GRANTED.

² Alt A, Potthast H, Moessinger J, Sickmüller B, Oeser H. Eur J Pharm Biopharm. 2004 Jul;58(1):145-50

³ Drugs at the FDA (Betapace Label)

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/s/

SANDRA SUAREZ
09/18/2014

ANGELICA DORANTES
09/18/2014

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

NDA Number	205-108
Product name, generic name of the active, and dosage form and strength	Sotalol hydrochloride Oral Solution, 5 mg/mL
Submission date	Dec. 23, 2013
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
Applicant	Arbor Pharmaceuticals, LLC
Medical Division	DCP
Type of Submission	505(b)(2)
Biopharmaceutics Reviewer	Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

Background

The proposed drug product, Sotylize Oral Solution, contains the active ingredient sotalol hydrochloride USP, a pharmacological agent known as a beta-adrenergic blocking agent. This 505 (b)(2) submission makes reference to the compounded syrups of two FDA approved products, 1) Betapace Tablets (NDA 19-865) which has been on the US market since 1992 and is indicated for the treatment of documented life-threatening ventricular arrhythmias and, 2) Betapace AF (NDA 21-151) approved in 2000. It is indicated for the maintenance of normal sinus rhythm. Sotalol Hydrochloride Oral will be indicated for the same conditions as Betapace and Betapace AF.

In accordance to 21 CFR 320.22 (b) (3), the Applicant is requesting a waiver of the required BA/BE studies. The data submitted to support the biowaiver are summarized as follows:

1. Data supporting the claim that the proposed product contains an active ingredient in the same concentration and dosage form as an FDA-approved reference product.

2. Data supporting the claim that the proposed product contains no inactive ingredients or change in formulation that may significantly affect absorption of the active ingredient.

The following potential review issues have been identified:

- Since the approved labeling for Betapace and Betapace AF Tablets do not contain clinical information (e.g., PK, BA, or efficacy/safety) on the resulting extemporaneous compounding solution (reference drug product), can either of these compounding solutions be used as an acceptable listed drug product for this 505(b)(2) NDA submission?
- Given that the dosage form of the approved product is an immediate release oral tablet, is the Applicant relying on the appropriate regulations for the BE waiver request (e.g. 21 CFR 320.22 (b)(3))?

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

A. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		X	NA. This is an oral solution.
2.	Is the dissolution test part of the DP specifications?		X	NA
3.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		X	NA
4.	Is there a validation package for the analytical method and dissolution methodology?			NA
5.	Does the application include a biowaiver request?	X		
6.	Is there information/data supporting the biowaiver request?	X		There is a formal biowaiver request included in this submission. The biowaiver makes reference to CFR 320.22 (b) 3.

7.	Is there enough information to assess the extended release designation claim?		X	<p>Applicant cites 21 CFR 320.22 (b) (3). The proposed drug product should meet the following requirements:</p> <ol style="list-style-type: none"> 1. Be an oral solution 2. Contain an active ingredient in the same concentration and dosage form as an FDA-approved reference product 3. Contain no inactive ingredients or change in formulation that may significantly affect absorption of the active ingredient <p>Additional information/data included:</p> <ul style="list-style-type: none"> • Justification on the lack of clinical impact due to difference in osmolality between the reference drug (compounded syrup) and the product under review • Dissolution profiles for the approved tablets supporting rapid dissolution • Data justifying the claim that the compounded (reference) syrup is a true solution (see attached power point presentation).
4.	Does the application include an IVIVC model?		X	
5.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	NA
6.	Is there any in vivo BA or BE information in the submission?		X	
7.	Is there any design space proposed using in vitro release as a response variable?		X	This submission does not have QbD elements.

8.	Is the control strategy related to in vitro drug release?		X	NA
B. Filing Conclusion				
	Parameter	Yes	No	Comment
9.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		The NDA is fileable from Biopharmaceutics Perspective
10.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
12.	Are there any potential review issues identified?	X		<p>Potential Review Issues:</p> <ul style="list-style-type: none"> ➤ Since the approved labeling for Betapace and Betapace AF Tablets do not contain clinical information (e.g., PK, BA, or efficacy/safety) on the resulting extemporaneous compounding solution, can either of these compounding solutions be used as an acceptable listed drug product for this 505(b)(2) NDA submission? ➤ Given that the dosage form of the approved product is an immediate release oral tablet, is the Applicant relying on the appropriate regulations for the BE waiver request (e.g. 21 CFR 320.22 (b)(3))?

13.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		➤ It is noted that the formulations of the to-be-marketed (TBM) product and the formulation of the product used in the in vitro pH and osmolality testing are different. Therefore, provide pH and osmolality information for the formulation of the proposed TBM drug product.
14.	Are there any internal comment to other disciplines:		X	Refer to the attached power point slides for the comments sent to the Regulatory Policy Agents.

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Date

NDA 205-108

Sotalol Hydrochloride Oral Solution (5
mg/mL)

Arbor Pharmaceuticals, LLC

ONDQA/Biopharmaceutics Review
Filing Meeting

Sandra S. Sharp, PhD.

Background

- This is a 505(b)(2) NDA which relies on:
 - Betapace Syrup 5 mg/mL compounded from Betapace 120 mg tablets (NDA 19-865)
 - Betapace tablets 80 mg, 120 mg, 160 mg, 240 mg, and 320 mg approved by FDA on Oct 1992.
 - Betapace is indicated for the treatment of documented ventricular arrhythmias,
 - Betapace AF Syrup 5 mg/mL compounded from Betapace AF 120 mg tablets (NDA 21-151)
 - Betapace AF tablets 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 160 mg approved by FDA on Feb 2000.
 - Betapace AF is indicated for the maintenance of normal sinus in patients with symptomatic AFIB/AFL who are currently in sinus rhythm.

Background, cont.

- Sotalol is considered a highly soluble and permeable drug substance.
- The oral BA of sotalol following administration of the tablets was 90-100%.
- Betapace tablets are rapidly dissolving (e.g. > ^{(b) (4)} % in 15 min.

Biopharmaceutics Review

Focused on:

- The acceptability of the waiver request of the required BA/BE studies

Information needed to Support the Biowaiver

- Applicant cites 21 CFR 320.22 (b) (3)
The proposed drug product should meet the following;
 - Be an oral solution
 - Contain an active ingredient in the same concentration and dosage form as an FDA-approved reference product
 - Contain no inactive ingredients or change in formulation that may significantly affect absorption of the active ingredient

Data: Evidence for Same Concentration

Component	Quality Standard	Water Solubility ³	Function	Quantity/mL	
				To-be-marketed Sotalol Oral Solution Formulation	Prototype Formulation Used in In-Vitro Studies ²
Sotalol HCl	USP	(b) (4)	Active Ingredient	5 mg/mL	5 mg/mL
Sodium citrate (b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Citric acid (b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucralose	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium benzoate	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Grape flavor ¹	In-house	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purified water	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Data: Evidence for Same Dosage Form

Arbor (Potential Formulations) [†]		Beta	
Sotalol HCL Oral Solution (Sodium Benzoate as (b) (4))	Sotalol HCL Oral Solution (b) (4)	Extemporaneous Oral Solution	Oral Tablet
Sotalol HCl – 0.5%	Sotalol HCl – 0.5%	5 mg/mL Betapace	120 mg sotalol HCL/tablet [†]
(b) (4) Citrate (b) (4)	(b) (4) Citrate (b) (4)	Microcrystalline cellulose	Microcrystalline cellulose
Citric Acid – (b) (4)	Citric Acid – (b) (4)	Lactose	<div style="border: 2px solid red; border-radius: 50%; padding: 10px; display: inline-block;"> <p>Contains 1 mg/mL of sucrose (72 g/day dose)</p> </div>
Sucralose – (b) (4)	Sucralose – (b) (4)	Starch	
-	-	Stearic Acid	
-	-	Magnesium Stearate	
-	-	Colloidal silicon dioxide	
Grape Flavor – (b) (4)	Grape Flavor – (b) (4)	Colloidal silicon dioxide	Colloidal silicon dioxide (b) (4)
Purified Water	Purified Water		
Sodium Benzoate – (b) (4)	-		
-	(b) (4)		
-			

Is this a true solution?

Contains 1 mg/mL of sucrose (72 g/day dose)

Data: Evidence of True Solution

- The “*Preparation of Extemporaneous Oral Solution*” section of both Betapace and Betapace AF labeling states:
 - “*This compounding procedure results in a solution containing 5 mg/mL of sotalol HCl. The fine solid particles are the water-insoluble inactive ingredients of the tablets.*”
 - The Applicant prepared extemporaneous suspension (in triplicate) according to the label instructions.
 - For all tested samples the concentration ranged from 4.96-5.03 mg/mL)

Data: Evidence for the Absence of Inactive Ingredients or Change in Formulation Affecting BA

- *“the osmolarity of the proposed solution is within the range of the osmolarity of the marketed tablet and the osmolarity of the extemporaneously prepared solution, and*
- *the tablet’s disintegration and dissolution do not result in a significant lag in absorption”*

Data: Evidence of Similar Osmolarity

Undiluted Sample	pH	Osmolality (mOsm/kg)
Sotalol HCl Tablets in Deionized Water	5.4	39 ^a
Arbor's Sotalol HCl Oral Solution ^c	5.1	212
Sotalol <i>Extemporaneous Oral Solution</i>	2.4	2860 ^b

- a- Result below the calibrated range of the instrument of 50 to 850 mOsm/kg.
- b- Initial result was 715 mOsm/kg and was corrected for the 1:4 dilution with water that was required to obtain a result within the calibrated range of the instrument of 50 to 850 mOsm/kg.
- c- The formulation evaluated in DP2012-353 was Arbor's Sotalol Oral solution prototype formulation Batch SOT-007 as described in Table 1.



Data: Rapid Dissolution and Disintegration

➤ Tablets dissolved (^{(b) (4)} %) in less than 10 min using 0.1 N HCl, pH 4.5 and paddle, 50 rpm.

➤ Tablets dissolved in less than 5 min

Summary

- NDA is fileable from Biopharmaceutics perspective.
- Potential Review Issues:
 - Since the extemporaneous compounding solutions were not tested in pivotal PK and/or clinical trials, can these solutions be used as an acceptable listed (reference) product for this 505(b)(2) submission?
 - Is the Applicant relying on the appropriate regulations for the BE waiver request (e.g. 21 CFR 320.22 (b) (3))?

Is the compounding solution an appropriate listed (reference) product for this 505 b2 submission -Response from the Lawyer

- “The compounded syrup itself is not a listed drug, and, therefore, the 505(b)(2) applicant for sotalol oral solution (NDA 205108) cannot rely on the compounded syrup as a listed drug.
- The 505(b)(2) application can rely however, on the Agency’s findings of safety and effectiveness for the listed drugs, Betapace IR Tablets (NDA 19865) and/or Betapace AS Tablets (NDA 21151); and
- It can rely for approval on the findings described in the product labeling for these listed drugs (including information on the compounded syrup) to the extent it is scientifically relevant”.

Is the Applicant relying on the appropriate regulations for the BE waiver request (e.g. 21 CFR 320.22 (b) (3))

- “The 505(b)(2) proposed product does not appear to satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR 320.22 (a)(b). Specifically, the proposed product does not have the same dosage form as the drug product that is the subject of an approved application. We recommend proceeding under 21 CFR 320.24(b)(6) (any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence). ---We have interpreted 320.24(b)(6) broadly such that regulation would be satisfied if the Division believes the scientific information/justification is adequate to support approval under the 505(b)(2) pathway”.

Comments to be conveyed to the Applicant

1. It is noted that the formulation of the to-be-marketed (TBM) product and the formulation of the product used in the in vitro pH and osmolarity testings are different. Therefore, provide pH and osmolarity information for the formulation of the proposed TBM drug product.

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/s/

SANDRA SUAREZ
02/17/2014

ANGELICA DORANTES
02/18/2014