

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205108Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



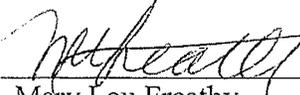
1.3. Administrative Information

PATENT CERTIFICATIONS

Paragraph I Certification

In accordance with Section 505(b)(2)(A)(i) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355), in the opinion and to the best knowledge of Arbor Pharmaceuticals, LLC, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Such certification is in accordance with Section 505(b)(2)(A)(i) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355, 21 CFR § 314.50(i)(ii)).



Mary Lou Freathy
VP, Regulatory, Quality, & Manufacturing



Date

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use**

NDA NUMBER

205108

NAME OF APPLICANT/NDA HOLDER

Arbor Pharmaceuticals LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Sotalol Hydrochloride Oral Solution

ACTIVE INGREDIENT(S)

Sotalol hydrochloride

STRENGTH(S)

5 mg/mL

DOSAGE FORM

oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Method of Use	
<i>Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input checked="" type="checkbox"/> Yes

6. Declaration Certification	
<p>6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)</p> 	<p>Date Signed</p> <p>12/20/2013</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>Mary Lou Freathy, Vice President of Regulatory, Quality, & Manufacturing</p>	
<p>Address</p> <p>980 Hammond Drive Suite 1250</p>	<p>City/State</p> <p>Atlanta GA</p>
<p>ZIP Code</p> <p>30328</p>	<p>Telephone Number</p> <p>470-235-2371</p>
<p>FAX Number (if available)</p>	<p>E-Mail Address (if available)</p> <p>mfreathy@arborpharma.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;"> Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer 1350 Piccard Drive, Room 400 Rockville, MD 20850 </p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 205108

SUPPL #

HFD # 110

Trade Name Sotylize

Generic Name sotalol hydrochloride oral solution 5 mg/mL

Applicant Name Arbor Pharmaceuticals, LLC

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The applicant requested and was granted a biowaiver. No studies were conducted.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Pediatric exclusivity was granted for a different product (different applicant) in 2000.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

interest provided substantial support for the study?

Investigation #1
!
! YES ! NO
! Explain: ! Explain:

Investigation #2
!
! YES ! NO
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Russell Fortney
Title: RHPM
Date: 10/2/14

Name of Office/Division Director signing form: Norman Stockbridge
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

RUSSELL FORTNEY
10/08/2014

NORMAN L STOCKBRIDGE
10/08/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 205108 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>								
Proprietary Name: Sotylize Established/Proper Name: sotalol hydrochloride Dosage Form: oral solution 5 mg/mL		Applicant: Arbor Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A								
RPM: Russell Fortney		Division: DCRP								
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 10/1/14</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>								
† Actions <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <td style="width: 70%;"> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is 7/27/14 </td> <td style="width: 30%;"> <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR </td> </tr> <tr> <td> <ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> </td> <td>None</td> </tr> <tr> <td> ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ </td> <td><input type="checkbox"/> Received</td> </tr> <tr> <td>❖ Application Characteristics³</td> <td></td> </tr> </table>			<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is 7/27/14 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 	None	❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	<input type="checkbox"/> Received	❖ Application Characteristics ³	
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is 7/27/14 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR									
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 	None									
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	<input type="checkbox"/> Received									
❖ Application Characteristics ³										

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 2 (<i>confirm chemical classification at time of approval</i>)									
<table style="width:100%; border:none;"> <tr> <td style="width:50%; border:none;"><input type="checkbox"/> Fast Track</td> <td style="width:50%; border:none;"><input type="checkbox"/> Rx-to-OTC full switch</td> </tr> <tr> <td style="border:none;"><input type="checkbox"/> Rolling Review</td> <td style="border:none;"><input type="checkbox"/> Rx-to-OTC partial switch</td> </tr> <tr> <td style="border:none;"><input type="checkbox"/> Orphan drug designation</td> <td style="border:none;"><input type="checkbox"/> Direct-to-OTC</td> </tr> <tr> <td style="border:none;"><input type="checkbox"/> Breakthrough Therapy designation</td> <td></td> </tr> </table>		<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rx-to-OTC full switch	<input type="checkbox"/> Rolling Review	<input type="checkbox"/> Rx-to-OTC partial switch	<input type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> Breakthrough Therapy designation	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rx-to-OTC full switch								
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<input type="checkbox"/> Breakthrough Therapy designation									
<table style="width:100%; border:none;"> <tr> <td style="width:50%; border:none;"> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) </td> <td style="width:50%; border:none;"> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) </td> </tr> <tr> <td style="border:none;"> Subpart I <input type="checkbox"/> Approval based on animal studies </td> <td style="border:none;"> Subpart H <input type="checkbox"/> Approval based on animal studies </td> </tr> </table>		NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520)	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)	Subpart I <input type="checkbox"/> Approval based on animal studies	Subpart H <input type="checkbox"/> Approval based on animal studies				
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520)	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)								
Subpart I <input type="checkbox"/> Approval based on animal studies	Subpart H <input type="checkbox"/> Approval based on animal studies								
<table style="width:100%; border:none;"> <tr> <td style="width:50%; border:none;"> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </td> <td style="width:50%; border:none;"> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </td> </tr> </table>		<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request	REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required						
<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request	REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required								
Comments:									
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates								
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No								
• Public communications (<i>approvals only</i>)									
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No								
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other –								
❖ Exclusivity									
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes								
❖ Patent Information (NDAs only)									
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.								
CONTENTS OF ACTION PACKAGE									
Officer/Employee List									
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included								
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included								

Action Letters	
✦ Copies of all action letters (including approval letter with final labeling)	Included
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> • Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (indicate date(s)) • Review(s) (indicate date(s)) 	Acceptable letter, 3/20/14, Review, 3/19/14
❖ Labeling reviews (indicate dates of reviews)	RPM: None DMEPA: <input checked="" type="checkbox"/> 3/20/14 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 10/8/14 SEALD: None CSS: None Patient Labeling: <input checked="" type="checkbox"/> 10/10/14
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	10/29/13
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	9/3/14
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics (<i>approvals only</i>)	
<ul style="list-style-type: none"> Date reviewed by PeRC 9/24/14 If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A (1 st cycle)
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 6/22/12
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	N/A
❖ Advisory Committee Meeting(s)	No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	10/17/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	10/16/14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	None
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	None
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	N/A (no clinical studies)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	N/A
❖ Risk Management	
<ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) 	N/A
<ul style="list-style-type: none"> REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) 	N/A
<ul style="list-style-type: none"> Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	None (no clinical studies)

Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No review
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No review
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> CMC 2/12/14, 6/23/14, 9/26/14; biopharm 2/18/14, 9/18/14
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> 2/4/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> OMPQ/Facilities 3/19/14

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	see page 78 of 6/23/14 review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: 3/19/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	N/A
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

PeRC PREA Subcommittee Meeting Minutes
September 24, 2014

PeRC Members Attending:

Lynne Yao

Wiley Chambers

George Greeley

Rosemary Addy

Lily Mulugeta

Melissa Tassinari

Colleen Locicero

Robert "Skip" Nelson

Gregory Reaman

Ruthie Davi

Peter Starke

Olivia Ziolkowski

PREA

9:10	NDA	205108	Sotylize (sotalol hydrochloride) Assessment	For the treatment of (b) (4) life-threatening ventricular arrhythmia and (b) (4) atrial fibrillation/atrial flutter
------	-----	--------	---	---



Sotylize (Full Waiver)

- Proposed Indication: For the treatment of (b) (4) life-threatening ventricular arrhythmia and (b) (4) atrial fibrillation/atrial flutter.
- *PeRC Recommendations:*
 - The PeRC noted that this sponsor was not statutorily required to submit an iPSP before the NDA submission. Therefore, the sponsor submitted an iPSP that was not previously reviewed by FDA as the pediatric plan.
 - The PeRC disagreed with the sponsor’s plan for waiver of studies in all pediatric populations. The PeRC noted that the sponsor intends to market this product (grape flavored solution) to pediatric patients for the proposed indications. However, the Division clarified that the sponsor conducted bioequivalence studies of their product to the crushed tablet (i.e., the approved pediatric formulation). Therefore, no pediatric studies are required and the PeRC agreed that the product is fully assessed for all pediatric populations down to birth.



(b) (4)

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/s/

GEORGE E GREELEY
10/07/2014

Fortney, Russell

From: McLamore-Hines, Sherita
Sent: Wednesday, October 01, 2014 11:11 AM
To: Fortney, Russell
Subject: RE: Sotalol Environmental Assessment

Yes ☹

Sherita D. McLamore-Hines, Ph.D.

Regulatory Review Chemist
Food and Drug Administration
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment I
Ph: 301-796-1710
Fax: 301-796-9747

From: Fortney, Russell
Sent: Wednesday, October 01, 2014 11:08 AM
To: McLamore-Hines, Sherita
Subject: Sotalol Environmental Assessment

Sherita,

From you review:

B. Environmental Assessment or Claim of Categorical Exclusion

The applicant claims the "Categorical Exclusion" for the environmental assessment for this NDA in accordance with 21CFR 25.31 (b). Based on 21CFR 25.31(a), a categorical exclusion should be granted as the action taken in this application **will increase** the use of the active moiety. Additionally, in accordance with 21CFR 25.15 (d), the applicant indicates that no extraordinary conditions exist and the drug substance is not derived from any wild source plant or animal material.

Is that supposed to be "will not increase"?

-Russell

From: [Knight, Yvonne](#)
To: [Allison Lowry \(ALowry@arborpharma.com\)](mailto:Allison.Lowry@arborpharma.com)
Cc: [Knight, Yvonne](#)
Subject: Information Request for NDA 205108 (Prompt Response)
Date: Thursday, September 11, 2014 11:55:54 AM
Importance: High

Good morning Ms. Lowry,

We have the following information request concerning Arbor Pharmaceuticals' New Drug Application (NDA) NDA 205108. We request a response to this IR request by **COB Friday September 12, 2014**.

Our August 22, 2014 IR included the following comment:

In your June 18, 2014 response, you proposed to exclude (b)(4) testing from the drug product specification. Be advised that this proposal is not acceptable.

Update the drug product specification to include a test and acceptance criterion for

(b)(4).

In your August 22, 2014 response, you indicated that stability specification was updated to include a test and acceptance criterion for (b)(4) (i.e. NMT (b)(4) %). We request that you confirm that both the release and stability specifications have been updated to include a test and acceptance criterion for (b)(4) and that you provide updated final drug product specifications.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA

10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
09/11/2014

From: [Knight, Yvonne](#)
To: [Allison Lowry \(ALowry@arborpharma.com\)](mailto:Allison.Lowry@arborpharma.com)
Cc: [Knight, Yvonne](#)
Subject: Information Request for NDA 205108 (Prompt Response)
Date: Friday, August 22, 2014 7:00:10 AM
Importance: High

Good morning Ms. Lowry,

We have the following information request concerning Arbor Pharmaceuticals' New Drug Application (NDA) NDA 205108. We request a response to this IR request by **COB Friday August 22, 2014**.

1. In your June 18, 2014 response, you proposed to exclude (b)(4) testing from the drug product specification. Be advised that this proposal is not acceptable. Update the drug product specification to include a test and acceptance criterion for (b)(4).
2. We are unable to complete the review of your NDA because information requested of DMF (b)(4) on 05-13-2014 has not been provided by the DMF holders. Since approval of your NDA depends on the adequacy of these DMFs please request the DMF holders to respond promptly.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
08/22/2014



NDA 205108

INFORMATION REQUEST

Arbor Pharmaceuticals, Inc.
Attention: Alison Lowry, Director
Regulatory Affairs
980 Hammond Drive, Suite 1250
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sotalol Hydrochloride.

We also refer to your December 23, 2013, submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

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)
(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 their 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 (b) (4) mL contains 5 mg Sotalol HCl”. As the drug product is formulated as a 5 mg/mL, all labeling should be updated to reflect this concentration.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Acting Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

OLEN M STEPHENS
06/02/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205108

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Arbor Pharmaceuticals, LLC
6 Concourse Parkway
Suite 1800
Atlanta, GA 30328

ATTENTION: Allison Lowry
Director, Regulatory Affairs

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated and received December 23, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sotalol Hydrochloride Oral Solution, 5 mg/mL.

We also refer to your correspondence, dated and received December 26, 2013, requesting review of your proposed proprietary name, Sotylize. We have completed our review of the proposed proprietary name, Sotylize, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 26, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Bengtson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3338. For any other information regarding this application, contact Russell Fortney, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/20/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205108

**ACKNOWLEDGE CORPORATE
ADDRESS CHANGE**

Arbor Pharmaceuticals LLC
Attention: Ms. Tina Morton
Sr. Manager, Regulatory Affairs
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

Dear Ms. Morton:

We acknowledge your February 27, 2014 correspondence notifying the Food and Drug Administration (FDA) that the corporate address has been changed from

Arbor Pharmaceuticals LLC
980 Hammond Drive, Bldg. 2, Suite 1250
Atlanta, GA 30328

to

Arbor Pharmaceuticals LLC
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

for NDA 205108 for Sotalol Hydrochloride Oral Solution, 5 mg/mL.

We have revised our records to reflect this change.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Russell Fortney, R.Ph.
Regulatory Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
03/13/2014



NDA 205108

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Arbor Pharmaceuticals, LLC
Attention: Allison Lowry
980 Hammond Drive
Suite 1250
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated December 23, 2013, received December 23, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for sotalol hydrochloride oral solution (5 mg/mL).

We also refer to your amendments dated December 26, 2013, and February 20, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 23, 2014

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 22, 2014.

During our filing review of your application, we identified the following potential review issues:

1. The approved labeling for the listed drugs, Betapace and Betapace AF Tablets, does not contain clinical information (e.g., Pharmacokinetic, Bioavailability, or Efficacy/Safety) on the extemporaneously compounded solutions. The adequacy of your approach to establish a scientific bridge that justifies reliance on Betapace and Betapace AF to compare your proposed product with solution compounded from Betapace and Betapace AF tablets will be a review issue.
2. Given that the dosage form of the proposed listed product (Betapace Tablets) is an immediate release oral tablet, relying on 21 CFR 320.22 (b)(3) to support the biowaiver will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Please submit your Methods Validation Package to section 3.2.R.
2. It is noted that the to-be-marketed (TBM) product and the prototype formulation used in the *in vitro* testing for the determination of pH and osmolality are different (refer to Table 1, in section \NDA205108\0000\m1\us\112-oth-cor req-waiv-iviv-ba.pdf). Therefore, provide pH and osmolality information for the proposed TBM drug product formulation.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because an oral solution is a new dosage form, you must fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric

drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indications proposed in this application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Cardiovascular and Renal Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
02/26/2014



NDA 205,108

NDA ACKNOWLEDGMENT

Arbor Pharmaceuticals, LLC
Attention: Ms. Allison Lowry
Director, Regulatory Affairs
980 Hammond Drive, Suite 1250
Atlanta, GA 30328

Dear Ms. Lowry:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Sotalol Hydrochloride Oral Solution, 5 mg/mL

Date of Application: December 23, 2013

Date of Receipt: December 23, 2013

Our Reference Number: NDA 205108

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Russell Fortney, R.Ph.
Regulatory Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
12/30/2013

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2015. See instructions for OMB Statement, below.		
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET	
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm		
1. APPLICANT'S NAME AND ADDRESS ARBOR PHARMACEUTICALS Allison Lowry 980 Hammond Drive Suite 1250 Atlanta GA 30328 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 205-108
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 678-334-2428		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME sotalol oral solution		6. USER FEE I.D. NUMBER PD3013881
7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO PRIORITY REVIEW VOUCHER NUMBER:		
8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY		
9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO If a waiver has been granted, include a copy of the official FDA notification with your submission.		
Privacy Act Notice: This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. 552a. The collection of this information is authorized by 21 U.S.C. 371, 379, 379e, 379h, 379h-1, 379j, 379j-12, 379j-21, 387s, and 393(d)(2); 42 U.S.C. 263b(r)(1); 5 U.S.C. 301 and 552; and 42 U.S.C. 3101. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory. Failure to supply the information could prevent FDA from processing user fee payments. Additional detail regarding FDA's use of information is available online: http://www.fda.gov/RegulatoryInformation/FOI/PrivacyAct/default.htm .		
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850		
Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850		
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.		
PRINTED NAME AND SIGNATURE OF AUTHORIZED	TITLE	DATE

REPRESENTATIVE	<i>Allison Frumy</i>	<i>Director, RA</i>	<i>12/23/13</i>
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION			
\$1,084,550.00			
Form FDA 3397 (03/12)			

Allison Lowry

From: paygovadmin@mail.doc.twai.gov
Sent: Thursday, December 19, 2013 10:10 AM
To: Allison Lowry
Subject: Pay.gov Payment Confirmation: FDA User Fees

Your payment has been submitted to Pay.gov and the details are below. If you have any questions or wish to cancel this payment, you will need to contact FDA User Fees at (301) 796-7200.

Application Name: FDA User Fees
Pay.gov Tracking ID: 25DDOVFK
Agency Tracking ID: 3013881

Account Holder Name: ARBOR PHARMACEUTICALS Transaction Type: ACH Debit Transaction Amount: \$1,084,550.00
Payment Date: Dec 20, 2013 Account Type: Business Checking Routing Number: (b)(4) Account Number:
*****4186

Transaction Date: Dec 19, 2013 10:09:59 AM Total Payments Scheduled: 1
Frequency: OneTime

THIS IS AN AUTOMATED MESSAGE. PLEASE DO NOT REPLY.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

P-IND 115232

MEETING MINUTES

Arbor Pharmaceuticals, Inc.
c/o Camargo Pharmaceutical Services, Inc.
Attention: Ruth Stevens, PhD, MBA
Chief Scientific Officer and Executive Vice President
9825 Kenwood Road
Suite 201
Cincinnati, OH 45242-6252

Dear Dr. Stevens:

Please refer to your Pre-Investigational New Drug Application (PIND) for sotalol oral solution.

We also refer to the meeting between representatives of your firm and the FDA on June 12, 2012. The purpose of the meeting was to discuss the requirements for a 505(b)(2) NDA for sotalol oral solution.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: P-IND Meeting

Meeting Date: June 12, 2012
Meeting Location: FDA White Oak Campus

Application Number: P-IND 115232
Product Name: Sotalol hydrochloride oral solution
Sponsor/Applicant Name: Arbor Pharmaceuticals, Inc.

Meeting Chair: Norman Stockbridge
Meeting Recorder: Russell Fortney

FDA ATTENDEES

Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Khin U, MD	Medical Reviewer
Tom Papoian, PhD	Pharmacology Team Leader
Elizabeth Hausner, DVM	Pharmacologist
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Russell Fortney	Regulatory Project Manager

Office of Clinical Pharmacology

Rajanikanth Madabushi, PhD	Team Leader
Peter Hinderling, MD	Reviewer

Office of New Drug Quality Assessment

Kasturi Srinivasachar, PhD	Chemistry Pharmaceutical Assessment Lead
Kareen Riviere, PhD	Biopharmaceutics Reviewer

Office of Orphan Product Development

Chip Startzman, MD

ARBOR PHARMACEUTICALS ATTENDEES

Laurence J. Downey, MD	VP, Medical and Scientific Affairs
Adel Gomez	Director, Manufacturing and Validation
Allison Lowry	Director of Regulatory Affairs

(b) (4)

BACKGROUND

Sotalol is currently approved as tablets and an injectable formulation for intravenous use in patients who are unable to take sotalol orally. The approved labeling for sotalol tablets includes instructions for compounding an extemporaneous oral solution using tablets. Arbor Pharmaceuticals is developing an oral solution formulation of sotalol hydrochloride. Preliminary responses to the sponsor's submitted questions were communicated to the sponsor prior to the meeting and are copied below, followed by any discussion that took place during the meeting.

DISCUSSION

The following questions were addressed:

Regulatory/Medical

1. Is the Agency in agreement with the 505(b)(2) regulatory pathway for the Sotalol HCl oral solution product?

Preliminary FDA response: It appears a 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which we consider to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act (in other words, an application approved under section 505(j) of the Act (i.e., ANDA, generic drug) may not be cited as a listed drug relied upon). The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you choose to rely on FDA's finding of safety and/or effectiveness for a listed drug(s) and you intend to use your proposed comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s), then you should use the specified listed drug(s) (rather than a bioequivalent ANDA product) as the comparator.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the FD&C Act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Additional discussion during meeting: No additional discussion.

2. At the time of approval, due to differences in dosing, safety information, and the requirement for a patient package insert for Betapace AF, the Betapace AF product was required to have a separate label from the Betapace product. In an effort to minimize confusion, Arbor is planning to submit one NDA with one label for the two indications, as currently exists for the sotalol HCl injection for intravenous (iv) use (NDA 22306; Academic Pharms; see Appendix 3 for Label). Does the Agency agree?

Preliminary FDA response: Yes. Please include in your proposed label for Sotalol HCl oral solution formula the Box Warning that is in the approved labeling for Sotalol HCl injection for intravenous use.

Additional discussion during meeting: No additional discussion.

3. Arbor is planning to submit a request for orphan drug designation for the sotalol HCl oral solution product for the treatment of ventricular arrhythmias and for the maintenance of normal sinus rhythm in patients who are unable to take sotalol HCl tablets orally. While the approved labeling for both Betapace and Betapace AF contains a procedure to prepare an extemporaneous oral solution by compounding, this extemporaneous procedure lacks robustness and in-process controls, and unnecessarily exposes patients to non-soluble excipients (unrelated to the action of the API). The proposed Sotalol HCl oral solution product will provide the appropriate level of control (eg, robustness, content uniformity) compared to the pharmacy-compounded product, making a major contribution to patient care while providing efficacy and safety comparable to the previously approved drug. Does the Agency agree with Arbor's plan to submit a request for orphan drug designation for the Sotalol HCl oral solution product?

Preliminary FDA response: You may request orphan drug designation for sotalol HCl for the treatment of ventricular arrhythmias and for maintenance of normal sinus rhythm in patients unable to take sotalol tablets orally. However, there are review issues with such an application including the following:

- A. It is not clear why this product would not be effective in patients who could take sotalol tablets. It would appear that the disease or condition that should be the subject of the orphan drug designation request should be ventricular arrhythmia.
- B. We usually designate the active moiety. In this case, sotalol tablets are already approved for the treatment of ventricular arrhythmias. In order for sotalol oral solution to be eligible for orphan drug designation, you must provide a plausible hypothesis for the clinical superiority of oral solution over tablets (superior safety, efficacy, or a major contribution to patient care). This will be a review issue.

Additional discussion during meeting: No additional discussion.

4. The Pediatric Research Equity Act (PREA) (21 USC § 355c) requires that NDAs for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless the applicant has obtained a waiver or deferral. Arbor plans to submit a request for orphan drug designation for the Sotalol HCl oral solution product for the maintenance of normal sinus rhythm (delay in time to recurrence of AFIB/AFL) and for the treatment of documented life-threatening ventricular arrhythmias. The requirements of PREA will not be applicable if orphan drug designation is granted. Does the Agency concur?

Preliminary FDA response: If you are granted orphan drug designation for Sotalol HCl oral solution for the maintenance of normal sinus rhythm and for the treatment of documented life-threatening ventricular arrhythmias and you subsequently receive marketing approval for the designated drug for the designated disease or condition, then you would be exempt from PREA.

Additional discussion during meeting: No additional discussion.

Clinical Pharmacology

5. Arbor intends to submit a bioavailability (BA)/bioequivalence (BE) waiver request for the Sotalol HCl oral solution product (5 mg/mL) with the application, and supportive data as it meets the provisions established in 21 CFR 320.22. Does the Agency agree with the proposed BA/BE waiver request?

Preliminary FDA response: No. We do not agree with your plan to request a waiver of BA/BE studies for your proposed product for the following reasons:

- A. The provisions established in 21 CFR 320.22 (b)(3) do not apply in this situation since the Betapace and Betapace AF extemporaneous compounded formulations are suspensions rather than true solutions.
- B. Your proposed product will have a markedly different osmolarity compared to the Betapace and Betapace AF extemporaneous compounded formulations, potentially impacting the bioavailability of sotalol HCl.

Additional discussion during meeting: Dr. Hinderling reiterated that the Agency's concern is with the osmolarity of the sponsor's proposed solution, which is considerably lower than that of the extemporaneous solution. However, if the sponsor can show that a) 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 b) the tablet's disintegration and dissolution do not result in a significant lag in absorption this concern may be mitigated. Dr. Madabushi added that it would be helpful if the sponsor could provide a comparison of the pH for the marketed sotalol tablet in water, the extemporaneous solution, and the sponsor's proposed solution.

Post-meeting FDA Comment: The sponsor should provide additional data demonstrating that the extemporaneously prepared formulation is a true solution (e.g. more than ^(b)₍₄₎% of the drug product is dissolved before dispensing it).

6. The Betapace and Betapace AF labeling includes dosing information for the pediatric population. The 5 mg/mL extemporaneously compounded oral solution presented in the labeling is prepared from five 120 mg tablets in 120 mL solution. This compounded formulation was used in the clinical pharmacology studies conducted in pediatric patients to provide dosing information for LD labeling. Arbor plans to establish similar in vitro solubility profiles between its Sotalol HCl Oral Solution (5 mg/mL) and the two extemporaneously prepared oral solutions (5 mg/mL prepared from five 120 mg tablets in 120 mL solution and 5 mg/mL prepared from five 160 mg tablets in 160 mL solution) to bridge to clinical data. Does the Agency find this approach acceptable given that the 160 mg tablet is the LD for Betapace and Betapace AF?

Preliminary FDA response: No. It is not acceptable to use in vitro testing to compare the proposed product to extemporaneously compounded Betapace and Betapace AF. In vitro solubility profiles are drug substance dependent and are not impacted by formulations changes. Dissolution testing may be used to evaluate the in vitro performance of solid dosage forms. However, dissolution testing is not appropriate in this situation since your proposed product is a solution.

Additional discussion during meeting: No additional discussion.

Clinical

7. As Arbor is requesting a BA/BE waiver, and as the proposed Sotalol HCl Oral Solution will be administered at the same dosage concentration, for the same duration, and for the same indications as the extemporaneously compounded oral solution prepared from the LD Betapace tablet ((b) (4) Betapace AF tablet), no clinical studies are currently planned. Does the Agency find this approach acceptable?

Preliminary FDA response: No. First, we not agree with your plan to request a waiver of BA/BE studies for your proposed product (Please see response to Question 5).

Secondly, there are other issues to be considered as follows:

- FDA has implemented the biopharmaceutics classification system (BCS) to allow a waiver of *in vivo* BE testing for BCS class I, high-solubility, high-permeability drugs in IR fast-dissolving solid dosage forms.¹ It is generally recognized that if a drug has (b) (4)% fraction dose absorbed (F_{abs}), the drug must be highly permeable in the human jejunum (P_{eff}),² although actual permeability data may not be available. However, in the case of sotalol, this direct correlation between intestinal permeability and fraction dose absorbed does not hold true, since sotalol has low transepithelial permeability across Caco-2 cell monolayers³ while (b) (4)% extent of absorption was reported for sotalol.^{4,5} The high F_{abs} accompanies high P_{eff} for sotalol, not in the jejunum, but somewhere along the distal small intestinal regions which compensates for its low permeability in the proximal segments,⁶ resulting in its high extent of absorption, albeit with a relatively long T_{max} of 2.5 to 4 hours.
- The proposed Sotalol HCL solution has a very low osmolality (215 mOsm/kg) compared to the extemporaneously prepared suspensions from sotalol tablets (about 1700 mOsm/Kg for the Ora-

¹ CDER/FDA. Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system; Center for Drug Evaluation and Research: 2000.

² Chen, M.-L.; Yu, L. The use of drug metabolism for prediction of intestinal permeability. *Mol. Pharmaceutics* 2009, 6, 74–81.

³ Yang, Y.; Faustino, P. J.; Volpe, D. A.; Ellison, C. D.; Lyon, R. C.; Yu, L. X. Biopharmaceutics classification of selected betablockers: solubility and permeability class membership. *Mol. Pharmaceutics* 2007, 4, 608–614.

⁴ Hanyok, J. Clinical pharmacokinetics of sotalol. *Am. J. Cardiol.* 1993, 72, 19A–26A.

⁵ Funck-Brentano, C. Pharmacokinetic and pharmacodynamic profiles of d-sotalol and d,l-sotalol. *Eur. Heart J.* 1993, 14, 30–35.

⁶ Dahan A, Miller HM, Hilfinger JM, Yamashita S, Yu LX, Lennernas H, Amidon GL. High-permeability criterion for BCS classification: segmental/pH dependent permeability considerations. *Mol. Pharmaceutics* 2010, 7, 1827-1834.

Blend suspensions and about 4000 mOsm/kg for the Simple Syrup suspensions). The normal osmolality of gastrointestinal secretions is 100 ~ 400 mOsm/kg. While the low osmolality of the proposed Sotalol HCl solution may have the advantage of improved absorbability from the gut, the markedly low osmolality may alter the permeability dynamics of sotalol to faster/earlier absorption in the jejunum (instead of the distal small intestines) leading to shorter T_{max} and, possibly also, a higher C_{max} . The clinical implication of this altered pharmacokinetics would be an increased risk of potential toxic effects (torsade de pointes). This consideration becomes particularly important in the case of patients who may be administered oral sotalol through enteral feeding tubes which may deliver a formulation of sotalol that is potentially rapidly absorbed and, therefore, may require dose adjustments.

- Other factors to be considered when sotalol is available as a liquid solution formulation are: (i) viscosity of the solution (e.g., it may be too viscous for administration via fine bore tubes), (ii) pH of the Sotalol HCL solution (as sotalol has low permeability at pH 6.5 and 7.0, and relatively higher permeability at pH 7.5), (iii) possibility of “caking” in the tubes (e.g., observed with Augmentin) or bezoar formation (e.g., observed with sucralfate), and (iv) possibility of adsorption of active drug onto the plastic tubing resulting in reduced dose being delivered.

Additional discussion during meeting: The sponsor said they will investigate the caking and adsorption issues. Dr. Hinderling advised the sponsor to submit a proposal for Agency review prior to conducting the studies.

Nonclinical

8. As Arbor has provided data showing that the proposed Sotalol HCl Oral Solution contains excipients within the range of concentrations found in the IIG and does not contain any excipient that significantly affects drug absorption, no additional nonclinical studies are proposed. Arbor will provide data establishing similar in vitro solubility profiles between the proposed Sotalol HCl oral solution product and the extemporaneously compounded oral solution prepared from the LD (Betapace tablet [identical to Betapace AF tablet]). Does the Agency find this approach acceptable?

Preliminary FDA response: Yes.

Additional discussion during meeting: No additional discussion.

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/s/

NORMAN L STOCKBRIDGE
06/22/2012