CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-021

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-021 SUPPL # N/A HFD # 110

Trade Name Altace Tablets

Generic Name Ramipril

Applicant Name Cobalt Pharmaceuticals

Approval Date, If Known 2/27/07

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)(1)

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 sponsor has the "right of reference" to the RLD and has also submiited bioequivaence data to support approval of this application.

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?

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# 19-901 Altace Capsules

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:

NDA 19-901

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 ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

NDA 19-901

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

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

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

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in 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: Alisea Crowley
Title: Regulatory Health Project Manager
Date: 2/28/2007

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Norman Stockbridge
2/28/2007 07:48:54 AM

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

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
22-021

NAME OF APPLICANT / NDA HOLDER
Cobalt Pharmaceuticals

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)
To be determined

ACTIVE INGREDIENT(S)	STRENGTH(S)
Ramipril	1.25 mg, 2.5 mg, 5 mg and 10 mg

DOSAGE FORM
Tablets

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 file 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

PSC Media Arts (301) 443-1090 EF

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?	☐ Yes ☐ 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?	☐ Yes ☐ 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).	☐ Yes ☐ 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.)	☐ Yes ☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes ☐ 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.)	☐ Yes ☐ 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?	☐ Yes ☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes ☐ 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.)	☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

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?	☐ Yes ☐ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ 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 approved 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. ☒ Yes

6. Declaration Certification

6.1 ***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.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed

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).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Dr . James Parker	
Address 93 Birch Hill Road	City/State Stow/MA
ZIP Code 01175-1308	Telephone Number 978-897-8404
FAX Number *(if available)* 978-461-0333	E-Mail Address *(if available)*

COBALT

STATEMENT PURSUANT TO SECTION 505(b)(2)(B)
of the Federal Food, Drug and Cosmetic Act

Re: U.S. Patent No. 5,403,856

In accordance with the Federal Food, Drug, and Cosmetic Act, a statement pursuant to section 505(b)(2)(B) of the Federal Food, Drug, and Cosmetic Act is hereby provided for our 505(b)(2) New Drug Application for Ramipril Tablets, 1.25mg, 2.5mg, 5mg and 10mg.

U.S. Patent No. 5,403,856 claims a method of use, use code U-71, "*method of treatment of heart failure*" for which Cobalt Pharmaceuticals, Inc. is not seeking approval in this application.

Ms. Tirtho Uppal
VP, R&D and Regulatory Affairs

Aug 25/05
Date

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

COBALT

PATENT CERTIFICATION

Paragraph III Certification

Re: U.S. Patent 5,061,722

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our New Drug Application submitted under Section 505(b)(2) for Ramipril Tablets, 1.25, 2.5, 5, 10mg.

Cobalt Pharmaceuticals Inc. hereby certifies that, in its opinion and to the best of its knowledge based upon listings in the FDA's Orange Book electronic version, copy attached (Approved Drug Products with Therapeutics Equivalence), U.S. Patent No. 5,061,722 will expire on October 29, 2008 for the 1.25mg and on October 19, 2008 for the 2.5, 5 and 10 mg

This certification is made in accordance with Section 505(b)(2)(A)(iii) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.50(i)(1)(i)(A)(3).

Ms. Tirtho Uppal
VP, R&D and Regulatory Affairs

Jan 9/06
Date

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

COBALT
PHARMACEUTICALS INC.

Debarment Certification Statement

Cobalt Pharmaceuticals hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Ms. Tirtho Uppal
VP, R&D and Regulatory Affairs
Cobalt Pharmaceuticals

March 23/06
Date

Dr. James M. Parker
US Agent for Cobalt Pharmaceuticals
Strategic Bioscience Corporation

Date

6500 KITIMAT ROAD
MISSISSAUGA, ONTARIO
CANADA, L5N 2B8

T 905 814 1820 T 1 866 254 6111 F 905 814 8696

Comment 4:

Financial Disclosure Form 3455.

Response 4:

A copy of the Financial Disclosure Form 3455 along with an attachment are presented in the following pages. Please note, checkboxes have not been marked off as applicable since the individuals named in the attachment have not participated in financial arrangements or hold financial interests.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-021 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: January 30, 2006 **PDUFA Goal Date:** February 28, 2007

HFD 110 **Trade and generic names/dosage form:** Altace (ramipril) 1.25, 2.5, 5 and 10 mg Tablets

Applicant: Cobalt Pharmaceuticals **Therapeutic Class:** ACE-I

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ✓ **Yes. Please proceed to the next question.**
- ☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 3

Indication #1: Hypertension

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ✓ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ✓ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ✓ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Alisea Crowley, Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: __Reduction in Risk of Myocardial Infarction, Stroke and death from Cardiovascular Disease__

Is this an orphan indication?

PREA does not apply. Skip to signature block.

X **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

✓ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
✓ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ection D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Alisea Crowley, Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #3: Heart Failure Post Myocardial Infarction

Is this an orphan indication?

PREA does not apply. Skip to signature block.

X **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

✓ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
✓ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Alisea Crowley, Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Edward Fromm
2/26/2007 10:05:38 AM
E.Fromm for A. Crowley

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See page attached (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study See page attached (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Tirtho Uppal	VP, RD & Regulatory Affairs
FIRM / ORGANIZATION: Cobalt Pharmaceuticals	
SIGNATURE: D. Hillman for Tirtho Uppal	DATE: Mar 23/06

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

PSC Media Arts (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
see page attached	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Tirtho Uppal	Vice President, R&D and Regulatory Affairs
FIRM / ORGANIZATION: Cobalt Pharmaceuticals	
SIGNATURE: Tirtho Uppal	DATE: Aug 25/05

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

1.3.a.6 Financial Disclosure Information

Form FDA 3454 has been provided.

Attachment to Form FDA 3454
Certification: Financial Interests and Arrangements of Clinical Investigators

List of Investigators

A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Ramipril 10 mg Tablets Versus Altace® 10 mg Capsules In Normal Healthy Non-Smoking Male and Female Subjects for the USA, Study Number ——

Principal Investigators: ——————————
Sub-Investigators: ——————
——————

A Two-Way Crossover, Open-Label, Single-Dose, Fed, Bioequivalence Study of Ramipril 10 mg Tablets Versus Altace® 10 mg Capsules In Normal Healthy Non-Smoking Male and Female Subjects for the USA, Study Number ——

Principal Investigators: ——————————
Sub-Investigators: ——————
——————

A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Bioequivalence Study of Ramipril 1.25 mg Tablets Versus Altace® 1.25 mg Capsules In Normal Healthy Non-Smoking Male and Female Subjects for the USA, Study Number——

Principal Investigators: ——————————
Sub-Investigators: ——————
——————

CERTIFICATION / DISCLOSURE OF FINANCIAL INTERESTS AND ARRANGEMENTS

To be completed by Investigators/Sub-investigators in compliance with FDA regulations

A. For **Study** ——— (drug name: Ramipril Tablets; dose: 10 mg; dosing conditions: Single-Dose, Fasting) by the **Sponsor** (Cobalt Pharmaceuticals Inc.), I hereby certify that **my spouse, dependent children and I:**

TRUE	FALSE	
☑	☐	Have not participated in any financial arrangement with the sponsor of the clinical trial, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. **Compensation affected by the outcome of clinical studies** means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.
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B. For any item(s) above that I checked "**FALSE**", **I hereby disclose to have such financial arrangements/interests.** I am therefore **attaching the details** (please see attachment), clarifying the size and the nature of the said financial arrangements/interests.

C. I also agree to promptly update my financial disclosure information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

NAME & SIGNATURE of Investigator/ Sub-investigator — **Date (mm-dd-yyyy)**

To be completed by ——— Senior Management:
(if Investigator/Sub-investigator discloses any financial arrangements/interests, i.e., if any item(s) is/are checked "FALSE")

The following steps will be taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments:
(☐ - please see attachment)

NAME & SIGNATURE of ——— Senior Management — **Date (mm-dd-yyyy)**

CERTIFICATION / DISCLOSURE OF FINANCIAL INTERESTS AND ARRANGEMENTS

To be completed by Investigators/Sub-investigators in compliance with FDA regulations

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(if Investigator/Sub-investigator discloses any financial arrangements/interests, i.e. if any item(s) is/are checked "FALSE")

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NAME & SIGNATURE of——— Senior Management **Date (mm-dd-yyyy)**

CERTIFICATION / DISCLOSURE OF FINANCIAL INTERESTS AND ARRANGEMENTS

To be completed by Investigators/Sub-investigators in compliance with FDA regulations

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NAME & SIGNATURE of Investigator/ Sub-investigator — **Date (mm-dd-yyyy)**

To be completed by ——— Research Senior Management:
(if Investigator/Sub-investigator discloses any financial arrangements/interests, i.e., if any item(s) is/are checked "FALSE")

The following steps will be taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments:
(☐ - please see attachment)

NAME & SIGNATURE of ——Senior Management — **Date (mm-dd-yyyy)**

CERTIFICATION / DISCLOSURE OF FINANCIAL INTERESTS AND ARRANGEMENTS

To be completed by Investigators/Sub-investigators in compliance with FDA regulations

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NAME & SIGNATURE of Investigator/ Sub-investigator — Date (mm-dd-yyyy)

To be completed by ——— Senior Management if Investigator/Sub-investigator discloses any financial arrangements/interests i.e. if any item(s) is/are checked "FALSE".

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NAME & SIGNATURE of ——— Senior Management — Date (mm-dd-yyyy)

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_____ _____

NAME & SIGNATURE of Investigator/ Sub-investigator **Date (mm-dd-yyyy)**

To be completed by ——— Senior Management
(if Investigator/Sub-investigator discloses any financial arrangements/interests; i.e. if any item(s) is/are checked "FALSE")

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(☐ - please see attachment)

_____ _____

NAME & SIGNATURE of ——— Senior Management **Date (mm-dd-yyyy)**

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NAME & SIGNATURE of Investigator/ Sub-investigator — Date (mm-dd-yyyy)

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NAME & SIGNATURE of ——— Senior Management — Date (mm-dd-yyyy)

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A. For **Study** —— (drug name: Ramipril 1.25 mg Tablets; dose: 1.25 mg; dosing conditions: Single-Dose, Fasting) by the **Sponsor** (COBALT PHARMACEUTICALS INC.), I hereby certify that **my spouse, dependent children and I**:

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☑	☐	Have no significant payments of other sorts from the sponsor of the clinical trial, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. **Significant payments of other sorts** means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for one year following the completion of the study.
☑	☐	Have no proprietary interest in the tested product. **Proprietary interest in the tested product** means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.
☑	☐	Have no significant equity interest in the sponsor of the clinical trial. **Significant equity interest in the sponsor of a covered study** means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in anon-publicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for one year following completion of the study.

B. For any item(s) above that I checked "**FALSE**", **I hereby disclose to have such financial arrangements/interests.** I am therefore **attaching the details** (please see attachment), clarifying the size and the nature of the said financial arrangements/interests.

C. I also agree to promptly update my financial disclosure information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

_____ _____

NAME & SIGNATURE of Investigator/ Sub-investigator **Date (mm-dd-yyyy)**

To be completed by —— Senior Management:
(if Investigator/Sub-investigator discloses any financial arrangements/interests, i.e., if any item(s) is/are checked "FALSE")

The following steps will be taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments:
(☐ - please see attachment)

NAME & SIGNATURE of —— Senior Management **Date (mm-dd-yyyy)**

CERTIFICATION / DISCLOSURE OF FINANCIAL INTERESTS AND ARRANGEMENTS

To be completed by Investigators/Sub-investigators in compliance with FDA regulations.

A. For **Study** —— (drug name: Ramipril 1.25 mg Tablets; dose: 1.25 mg; dosing conditions: Single-Dose, Fasting) by the **Sponsor** (COBALT PHARMACEUTICALS INC.), I hereby certify that **my spouse, dependent children and I:**

TRUE	FALSE	
☑	☐	Have not participated in any financial arrangement with the sponsor of the clinical trial, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. **Compensation affected by the outcome of clinical studies** means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.
☑	☐	Have no significant payments of other sorts from the sponsor of the clinical trial, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. **Significant payments of other sorts** means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for one year following the completion of the study.
☑	☐	Have no proprietary interest in the tested product. **Proprietary interest in the tested product** means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.
☑	☐	Have no significant equity interest in the sponsor of the clinical trial. **Significant equity interest in the sponsor of a covered study** means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in anon-publicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for one year following completion of the study.

B. For any item(s) above that I checked **"FALSE", I hereby disclose to have such financial arrangements/interests.** I am therefore **attaching the details** (please see attachment), clarifying the size and the nature of the said financial arrangements/interests.

C. I also agree to promptly update my financial disclosure information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

NAME & SIGNATURE of Investigator/ Sub-investigator **Date (mm-dd-yyyy)**

To be completed by —— Senior Management:
(If Investigator/Sub-investigator discloses any financial arrangements/interests, i.e., if any item(s) is/are checked "FALSE")

The following steps will be taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments:
(☐ - please see attachment)

NAME & SIGNATURE of —— Senior Management **Date (mm-dd-yyyy)**

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG OUALITY ASSESSMENT

Sponsor Name:	Cobalt Pharmaceuticals
Application Number:	NDA 22-021
Product Name:	Ramipril tablets
Teleconference Date and Time:	December 21, 2006, 15:30 EST
FDA Attendees:	Division of Pre-Marketing Assessment I Ramesh Sood, Ph.D.; Branch Chief Kasturi Srinivasachar, Ph.D.; Pharmaceutical Assessment Lead Prafull Shiromani, Ph.D.; Review Chemist Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality
External Attendees:	Tirtho Uppal, Director, Regulatory Affairs Marina Chaim, Regulatory Affairs Donna Hillier, Director, Regulatory Affairs Jake Edmondson, Regulatory Affairs Associate-Strategic Bioscience Corporation

1.0 BACKGROUND

Cobalt Pharmaceuticals, Inc. (Cobalt) submitted NDA 22-021 for ramipril tablets, proposed for the treatment of hypertension. Strategic Bioscience Corporation serves as the US Agent for Cobalt. Prafull Shiromani, Ph.D., Review Chemist of the Division of Pre-Marketing Assessment I requested a teleconference to clarify the need for and Cobalt's plan to submit of a letter of authorization for the Drug Master File for the drug substance, and to confirm the receipt of the office of biopharmaceutics recommendations for drug product dissolution specifications. The issues were discussed during the teleconference on December 21, 2006.

2.0 DISCUSSION

2.1 Letter of Authorization for drug substance DMF

Teleconference Discussion: FDA asked when a letter of authorization (LOA) for the ——————————could be expected to provide for adequate opportunity to review the drug substance prior to the action date of 2/28/07. FDA informed Cobalt that without the LOA, the materials contained in the DMF could not be reviewed, and this may result in approvability issues during this review cycle.

Cobalt indicated that due to contractual issues between Cobalt and the API supplier ——————— they could not specifically identify the date that the LOA would be submitted. Cobalt acknowledged and understood FDA's comments.

2.2 Dissolution Specifications

Teleconference Discussion: FDA asked if Cobalt had received the recommended dissolution specifications from the Office of Biopharmaceutics, of Q = ——————— minutes, instead of Cobalt's proposed specifications of Q = ——————— Cobalt indicated that they had received verbal notification of the recommendation, and were awaiting written notification. Further, Cobalt indicated that they were examining the existing data for justification of the dissolution specifications. FDA indicated that the recommendation would be included in the action letter, and no separate written notification would be sent. Cobalt and FDA discussed the impact of the specification changes on the existing stability program, and concluded that the new specifications would be used at the next primary stability time point, and that all data, using both the old and the new specifications, should be submitted by the end of January 2007 to be evaluated and used to assign the drug product expiry date. FDA requested that the data include all available dissolution profiles for primary stability batches, and include the mean, minimum and maximum values for each time point.

FDA requested that Cobalt submit electronic desk copies with a statement to the effect that the courtesy copies were identical to those submitted to the administrative file to facilitate the review and increase efficiency. FDA recommended that the PMQ be used as point of contact for these desk copies. Cobalt acknowledged and agreed with FDA's recommendations.

The teleconference ended amicably.

3.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

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/s/

Scott Goldie
1/8/2007 11:47:00 AM
PROJECT MANAGER FOR QUALITY

Ramesh Sood
1/8/2007 12:22:55 PM
CHEMIST

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, MAIL STOP 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE REVIEW #:** 2006-723
October 30, 2006	January 13, 2007	
DATE OF DOCUMENT:	**PDUFA DATE:**	
October 17, 2006	February 28, 2007	

TO: Norman Stockbridge, M.D.
Director, Division of Cardiovascular and Renal Products
HFD-110

THROUGH: Alina Mahmud, R.Ph., M.S., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Kimberly Pedersen, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:	**SPONSOR:** Cobalt Pharmaceuticals
Altace (Ramipril Tablets) ?5 mg, 2.5 mg, 5 mg, and 10 mg **NDA#: 22-021**	

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Altace from a safety perspective. This is considered a final decision. However, if the approval of this NDA is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Altace acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, MAIL STOP 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: November 14, 2006

NDA #: 22-021

NAME OF DRUG: Altace
(Ramipril Tablets)
1.25 mg, 2.5 mg, 5 mg, and 10 mg

NDA SPONSOR: Cobalt Pharmaceuticals

I. INTRODUCTION

This consult was written in response to a request from the Division of Cardiovascular and Renal Products (HFD-110) for a review of the proprietary name "Altace Tablets", regarding potential name confusion with other proprietary or established drug names. The sponsor is to market their ramipril tablets as "Altace" by means of a material licensing agreement with the innovator (King Pharmaceuticals). The sponsor submitted container labels, blister labels, carton and insert labeling for review from a medication error perspective.

PRODUCT INFORMATION

Altace contains ramipril in a tablet form for the reduction in risk of myocardial infarction, stroke, and death in patient with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (i.e. hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria). This tablet form is to be marketed in the same strengths as the currently marketed capsule dosage form (1.25 mg, 2.5 mg, 5 mg, and 10 mg). However, the labeling described the tablets as bioequivalent under fasted conditions. The rate of absorption is more rapid under fed conditions for the tablet formulation compared to the capsule. However, the medical officer determined the modest food effect on the ramipril concentrations and smaller effect on the active ramiprilat concentrations did not warrant any limitations to dosing. In addition, the Agency's Office of Clinical Pharmacology determined the products (capsule and tablet) to be bioequivalent. Thus, the dosing and indication of use will be the same as Altace capsules. The recommended starting dose for is 1.25 to 2.5 mg depending on concurrent disease and drug therapy. Maintenance doses range from 2.5 to 20 mg daily or twice daily depending on underlying conditions.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Altace to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The SAEGIS[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Altace tablets. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Altace tablets acceptable from a promotional perspective.

2. The Expert Panel identified nine additional established or proprietary names (Altace capsules, Ultane, Artane, Altocor, Altex, Aldex, Ultrase, Alteplase, and Activase) as having the potential for confusion with Altace tablets.

Table 1: Potential Look-Alike and Sound-Alike Names Identified for Altace tablets

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Altace Tablets	Ramipril Tablets, 1.25 mg, 2.5 mg, 5 mg and 10 mg	2.5 mg to 20 mg daily (as one dose or twice daily)	
Altace	Ramipril Capsules, 1.25 mg, 2.5 mg, 5 mg and 10 mg	2.5 mg to 20 mg daily (as one dose or twice daily)	LA/SA
Ultane	Sevoflurane Volatile Liquid for Inhalation, 250 mL	0.7% to 2% with nitrous oxide 1.4% to 3.3% without nitrous oxide	LA/SA
Artane (discontinued, but available as generic)	Trihexyphenidyl HCl Tablets and Elixir, 2 mg, 5 mg and 2mg/5 mL	3 mg to 15 mg daily, in divided doses administered TID to QID	LA/SA
Altocor (no longer marketed)	Lovastatin Tablets, 10 mg, 20 mg, 40 mg, and 60 mg	20 mg daily	LA/SA
Altex (PSE)	Guaifenesin and Pseudoephedrine HCl Tablets, 600 mg /120 mg	One tablet every 12 hours.	LA/SA
Aldex (no longer marketed)	Guaifenesin and Phenylephrine HCl Extended-release Tablets, 650 mg/25 mg	One tablet every 12 hours.	LA/SA

[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[5] www location http://www.uspto.gov/tmdb/index.html.
[6] Data provided by Thomson & Thomson's SAEGIS™ Online service, available at www.thomson-thomson.com

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Altace Tablets	Ramipril Tablets, 1.25 mg, 2.5 mg, 5 mg and 10 mg	2.5 mg to 20 mg daily (as one dose or twice daily)	
Ultrase	Amylase/Lipase/Protease Delayed-release Capsules, 20000 units, 4500 units, 25,000 units	One to three before or with meals and snacks.	LA/SA
Alteplase/Activase	Alteplase Powder for Solution, 50 mg and 100 mg	Patients > 67 kg: 100 mg Patients ≤ 67 kg: 1.25 mg/kg	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike)/SA (sound-alike).			

B. RESULTS OF FDA AERS DATABASE SEARCH

Altace capsules were approved in January 1991 and are currently marketed. Thus, DMETS reviewed the FDA Adverse Event Reporting System (AERS) database for confusion or error. DMETS used the tradename and verbatim letter string of "Altac%" and "Doxaz%" with the High Level Group Term (HLGT) of "medication errors" and Preferred Term of "pharmaceutical product complaint." This searched found fifteen actual or potential medication error cases. The potential cases involving Amaryl (n=2) and Amerge (n=1) were health care providers citing concerns with the look-alike similarities of these products with Altace. The remaining six cases were prescription misfills involving Artane (n=2, 1992 and 1995), Actos (1999), Amaryl (2000), Diabeta (2001), and alprazolam (2003). As these reports were limited in number, DMETS does not believe this proprietary name is significantly problematic.

The remaining six cases of an incorrect dose dispensed within the Altace product line. The majority of the reports did not indicate a reason for the error, but two noted the strength was typed in incorrectly. In light of the high sales volume of Altace and being that the last report was received in 2003, DMETS does not feel any revisions are necessary at this time.

C. SAFETY EVALUATOR RISK ASSESSMENT

The sponsor is adopting the currently marketed ramipril drug product name of Altace with the addition of the dosage form of "tablet." Prescription studies were not performed as this is virtually the exact same name with similar solid oral dosage form and strengths as the currently marketed Altace capsules. Therefore, postmarketing reporting would better reflect any potential for confusion when this tablet goes to market.

1. Name Confusion

In reviewing the proprietary name, the following nine names were identified as having the potential to be confused with the proposed name of Altace tablets: Altace capsules, Ultane, Artane, Altocor, Altex, Aldex, Ultrase, Alteplase, and Activase. Post-marketing reporting found that Artane (n=2 in 1992 and 1995) was confused with the currently marketed Altace capsules. In addition, post-marketing reports found that Altace capsules was confused or had the potential for confusion with alprazolam (n=1), Amaryl (n=3), Diabeta (n=1), Actos (n=1), and Amerge (n=1). As these reports were limited in number, DMETS will continue to monitor post-marketing reports for any potential safety signals. However, at this time, DMETS has no objections to the use of the name Altace Tablets from a safety perspective.

2. Differences in Bioequivalency with Altace Capsules

The letter dated September 22, 2006 from the King Pharmaceuticals remarks that the products are therapeutically the same; however, the insert labeling reads that [redacted]. The tablets have a quicker absorption under fed condition when compared to the capsules. The medical officer noted that the food effect was modest on the ramipril concentrations and smaller on the active ramiprilat concentrations; thus, necessitating no limitations to dosing relative to food. The Agency's clinical pharmacologist, described the capsule and tablet as bioequivalent [redacted]

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton labeling, unit dose blisters, and insert labeling, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. The established name is composed of the established name and the dosage form. Thus, relocate the dosage form of "Tablet" adjacent to ramipril to appear as such: "Ramipril Tablets"

2. The tablet colors of the currently marketed Altace capsules are identical to the color of the proposed Altace tablets for all strengths except for the 1.25 mg. The 1.25 mg capsule is yellow whereas the tablet is white. As there appears to be a color correlation with the color of the tablet/capsule to strength, DMETS recommends that the 1.25 mg strength tablet have the identical color as the approved capsules.

B. CONTAINER LABELS and CARTON LABELING

1. See General Comment A 1.

2. There appears to be a color correlation with the carton to tablet color of the approved capsules and this color correlation has carried over to the proposed tablet color. DMETS recommends this same color correlation be applied to the carton labeling and container labels of the tablet. The sponsor uses the same color for the 1.25 mg (yellow) capsule labeling as is used for Altace 1.25 mg capsule labeling. Therefore, the 2.5 mg strength would change from green to orange, the 5 mg from fuchsia to red and 10 mg from red to blue. This would also help to alleviate any potential confusion or selection error with the 10 mg tablet color of red, which overlaps with the 5 mg capsule (red).

3. Adjust the presentation of strength so that the "mg" is the same size, font, and color as the numerical strength.

4. Decrease the prominence of the company logo to lessen distraction from the key information points on the label (e.g. dosage form, strength).

5. The "Rx" of "Rx only" does not appear on the copies of the labels and labeling received. Please adjust for proper presentation on the final copy.

C. INSERT LABELING

1. See General Comment A 1.

2. Pharmacokinetics and Metabolism

The letter dated September 22, 2006 from the King Pharmaceuticals remarks that the products are therapeutically the same; however, the insert labeling reads [redacted]. The tablets have a quicker absorption under fed condition when compared to the capsules. The medical officer noted that the food effect was modest on the ramipril concentrations and smaller on the active ramiprilat concentrations; thus, necessitating no limitations to dosing relative to food. The Agency's clinical pharmacologist, described the capsule and tablet as bioequivalent [redacted]

3. Precautions (Information for Patients)

Post-marketing reporting found one recent case (2005) where a patient missed a dose and took a double dose the next day resulting in adverse events. [redacted]

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/s/

Kimberly Culley-Pedersen
2/15/2007 01:08:13 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/15/2007 02:26:05 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her absence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-021

Cobalt Pharmaceuticals Inc.
Attention: Ms. Tirth Uppal
6500 Kitimat Road
Mississauga, Ontario L5N 2B8
Canada

Dear Ms. Uppal:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ramipril 1.25, 2.5, 5 and 10 mg Tablets.

We also refer to your submission dated August 17, 2006, requesting regulatory guidance regarding the anticipated amendment to the pending NDA for Ramipril Tablets. We have reviewed the referenced material and have the following comments and recommendations for information.

) Because of the low solubility of the drug substance, it is important to determine the dissolution of the drug product as a function of the particle size. Based on the bioequivalence of the slower dissolving Altace® product, which is manufactured with the ———— drug substance, rapid dissolution should ensure that the ramipril tablets will be bioequivalent in vivo. The Office of Clinical Pharmacology recommendations that, in addition to the stability studies, you submit comparative dissolution studies using the following recommended dissolution method:

Apparatus:	Paddle Method
pH 1.2	0.1N HCl
Rpm:	50 rpm
Volume:	500 mL

The 10 mg lot D4004C should be used as the reference lot and one lot of each strength of product manufactured with the ———— drug substance should be used as the test lots. A complete dataset, as well as a tabulated summary dataset should be submitted for evaluation. An f2 analysis should be performed if possible.

If you have questions, please contact:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 796-1144

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

CC: James Parker, J.D., Ph.D.
U.S. Agent
Strategic Bioscience Corporation
93 Birch Hill Road
Stow, MA 01775
USA

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/s/

Norman Stockbridge
9/13/2006 03:57:01 PM

MEMORANDUM

To: Alisea Sermon
ODE I/Division of Cardiovascular and Renal Products

From: Lisa Hubbard, R.Ph.
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Date: August 28, 2006

Re: Comments on draft labeling:
NDA 22-021
Ramipril Tablets

DDMAC has reviewed the proposed package insert for NDA 22-021 (ramipril tablets) and offer the following comments with regard to promotional considerations:

Pharmacodynamics/Pharmacodynamics and Clinical Effects
Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes:

The proposed package insert contains data and a description of the Heart Outcomes Prevention Evaluation study (HOPE study) under the Pharmacodynamics and Clinical Effects subsection entitled, "Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes." It appears the applicant is prohibited from promoting the indication since the accompanying outcome indication has been removed from the indications and usage section of the package insert. DDMAC recommends ——— the HOPE study description from the Pharmacodynamics and Clinical Effects section of the package insert if the applicant is prohibited by exclusivity or patent protection from promoting the indication. As an example, DDMAC notes that the applicant did remove similar information from both the pharmacodynamics section and indications section of the proposed package insert as it relates to heart failure post myocardial infarction. DDMAC notes additional data are found in the ADVERSE REACTIONS /Hypertension /HOPE Study section of the package insert.

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/s/

Lisa Hubbard
8/28/2006 11:41:54 AM
DDMAC REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 22-021

Cobalt Pharmaceuticals Inc.
Attention: Ms. Tirth Uppal
6500 Kitimat Road
Mississauga, Ontario L5N 2B8
Canada

Dear Ms. Uppal:

Please refer to your January 10, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ramipril 1.25, 2.5, 5, and 10 mg Tablets.

We are reviewing the Chemistry, Manufacturing and Controls 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.

DRUG SUBSTANCE

1. **S.4.3 Validation of Analytical Procedures**

   [redacted]

2. **S.4.5 Justification of Specification**

   Please provide adequate justification for the [redacted]

3. **S.7.1 Stability Summary and Conclusions**

   a) Please indicate the lot no. of the drug substance incorporated into each of the stability batches.
   b) Please state if proposed re-test period is re-test or expiry.

c) [redacted]

DRUG PRODUCT

1. **P.1 Description and Composition of the Drug Product**

   There is no obvious reason for the score line on the tablet considering that the product is presented in all possible strengths. Please justify the presence of score line and provide data on the half tablet, such as content uniformity and dissolution of half tablets.

2. **P.2.3 Manufacturing Process Development**

   [redacted]

3. **P.3.3 Description of Manufacturing Process and Controls**

   [redacted]

4. **P.5.1 Specification**

   [redacted]

5. **P.5.6 Justification of Specification – Related Substances**

   [redacted]

6. **P.7 Container Closure System**

   a) Please certify that the contact materials of all the packages, (bottle, blister, liner) meet appropriate 21CFR food contact regulations.

b) Please provide container-closure moisture permeation data for the bottles as per USP <671>.

7. **P.8 Stability**

Please provide updated stability study reports on the Drug Substance and Drug Product by July 1, 2006, as agreed to at the pre-IND meeting with the Division of Cardiovascular and Renal Products – Cobalt (6/28/04).

8. **P.8.2 Post-approval Stability Protocol and Stability Commitment**

The proposed batches for subsequent years and the batch schedule (i.e., X – on request only) contradict the statement (signed by Mr. Damien Flynn-Arrow Generics, 04.08.2005) on the prior page that a production batch of each strength will be placed on stability every year.
In subsequent years the 1.25 mg (unique formulation) with 2.5 mg and 10 mg tablets should be placed on stability. The latter two strengths, would therefore, bracket the 5 mg strength. The stability packages should be the blister and at least one bottle configuration selected on a worst case scenario.

If you have any questions, please call:

Alisea Sermon, Pharm.D.
Regulatory Health Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

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

CC: James Parker, J.D., Ph.D.

U.S. Agent
Strategic Bioscience Corporation
93 Birch Hill Road
Stow, MA 01775
USA

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/s/

Edward Fromm
5/4/2006 01:37:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-021

Cobalt Pharmaceuticals Inc.
Attention: Ms. Tirth Uppal
6500 Kitimat Road
Mississauga, Ontario L5N 2B8
Canada

Dear Ms. Uppal:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ramipril 1.25, 2.5, 5 and 10 mg Tablets.

We also refer to your submission dated March 7, 2006, informing the Agency that Cobalt Pharmaceuticals, Inc. has received authorization from King Pharmaceuticals, Inc. to reference any pediatric studies submitted in the NDA 19-901 for Altace Capsules. This authorization also allows access to the underlying raw data that provide the basis for the reports of the investigations submitted within NDA 19-901.

We have reviewed the submission and agree that a waiver is justified for Ramipril Tablets for hypertension for the entire pediatric population because:

- data for the same active ingredient have been submitted and reviewed to assess the safety and effectiveness of the drug product in the pediatric population.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have questions, please contact:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 796-1144

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

CC: James Parker, J.D., Ph.D.
U.S. Agent
Strategic Bioscience Corporation
93 Birch Hill Road
Stow, MA 01775
USA

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/s/

Norman Stockbridge
4/6/2006 07:15:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-021

Cobalt Pharmaceuticals Inc.
Attention: Ms. Tirth Uppal
6500 Kitimat Road
Mississauga, Ontario L5N 2B8
Canada

Dear Ms. Uppal:

Please refer to your January 10, 2006 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ramipril 1.25, 2.5, 5 and 10 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 12, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, please contact:

Alisea Sermon, PharmD
Regulatory Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

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

CC: James Parker, J.D., Ph.D.
U.S. Agent
Strategic Bioscience Corporation
93 Birch Hill Road
Stow, MA 01775

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/s/

Norman Stockbridge
4/11/2006 12:21:18 PM

ATTACHMENT

MEMO OF FILING MEETING

DATE: **March 23, 2006**

BACKGROUND: **Cobalt Pharmaceuticals, Inc has submitted a 505(b)(2) application to market the product Ramipril Tablets, 1.25 mg, 2.5 mg, 5 mg, and 10 mg. The sponsor is seeking a hypertension claim for the proposed application.**

ATTENDEES:	**Norman Stockbridge, M.D., Ph.D.**	**Division Director**
	Abraham Karkowsky, M.D., Ph.D.	**Team Leader, Medical Officer**
	Charles Resnick, Ph.D.	**Team Leader, Pharmacologist**
	Carol Noory, Ph.D.	**Clinical Pharmacologist**
	Kasturi Srinivasachar, Ph.D.	**Team Leader, Chemist**
	Prafull Shiromani, Ph.D.	**Chemist**
	CT Viswanathan, Ph.D.	**DSI**
	Edward Fromm, B.S.	**Chief Project Manager**
	Alisea Sermon, Pharm.D.	**Project Manager**

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**	**Expected Completion Date:**
Medical:	**Abraham Karkowsky**	**October 15, 2006**
Secondary Medical:	**N/A**	
Statistical:	**N/A**	
Pharmacology:	**N/A**	
Statistical Pharmacology:	**N/A**	
Chemistry:	**Prall Shiromani**	**September 1, 2006**
Environmental Assessment (if needed):	**N/A**	
Biopharmaceutical:	**Carol Noory**	**July 31, 2006**
Microbiology, sterility:	**N/A**	**N/A**
Microbiology, clinical (for antimicrobial products only):	**N/A**	**N/A**
DSI:	**CT Viswanathan**	**October 15, 2006**
Regulatory Project Management:	**Alisea Sermon**	**October 15, 2006**
Other Consults: **DDMAC**	**Wayne Mitchell**	**October 15, 2006**

Per reviewers, are all parts in English or English translation? **X** YES ☐ NO

If no, explain:

CLINICAL FILE **N/A** ☐ REFUSE TO FILE ☐

- Clinical site inspection needed? ☐ YES ☐ NO

- Advisory Committee Meeting needed? YES, date if known _____ ☐ NO ☐

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY ☐ **X** FILE ☐ REFUSE TO FILE ☐
N/A

STATISTICS ☐ FILE ☐ REFUSE TO FILE ☐
N/A

BIOPHARMACEUTICS **X** REFUSE TO FILE ☐
FILE

- Biopharm. inspection needed? **X** NO ☐
  YES

PHARMACOLOGY ☐ FILE ☐ REFUSE TO FILE ☐
N/A

- GLP inspection needed? ☐ NO ☐
  YES

CHEMISTRY **X** REFUSE TO FILE ☐
FILE

- Establishment(s) ready for inspection? **N/A** ☐ NO ☐
  YES
- Microbiology **N/A** ☐ NO ☐
  YES

ELECTRONIC SUBMISSION:
Any comments: **None**

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

Yes The application is unsuitable for filing. Explain why:

Yes The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☐ Convey document filing issues/no filing issues to applicant by Day 74.

Alisea Sermon, Pharm.D.
Regulatory Project Manager, HFD-**110**

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/s/

Alisea Sermon
3/30/2006 09:47:08 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Drug Marketing, Advertising nd Communication

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Alisea Sermon
ODE I/Division of Cardio-Renal Products
(301) 796-1144

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3.13.06	N/A	22-021	Labeling Review for NDA	01.09.06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ramipril Tanlets	S	3, New formulation	09.01.06

NAME OF FIRM: Cobalt Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☒ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Labeling consult; Please access the EDR for all labeling submissions

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Alisea Sermon, PharmD	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Alisea Sermon
3/13/2006 02:06:54 PM

King Pharmaceuticals,™ Inc.
501 Fifth Street
Bristol, TN 37620

423-989-8172
Fax: 423-989-6133
thomas.rogers@kingpharm.com

March 3, 2006

Thomas K. Rogers, III, M.S.
Corporate Head, Regulatory Affairs

VIA EXPRESS MAIL

Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Drug Products, HFD-110
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road, Room 4160
Beltsville, MD 20705-1266

Re: Altace® (ramipril) Capsules
Authorization to Reference NDA 19-901

Dear Dr. Stockbridge :

King Pharmaceuticals, Inc. hereby authorizes the Food and Drug Administration to reference its NDA 19-901 for Altace® (ramipril) Capsules in so far as it supports the approval of NDA 22-021 for Ramipril Tablets submitted by:

Cobalt Pharmaceuticals, Inc.,
6500 Kitimat Road, Mississauga,
Ontario Canada, L5N 2B8

This authorization includes reference to any pediatric studies submitted in the NDA 19-901 for Altace Capsules. This authorization also provides FDA access to the underlying raw data that provide the basis for the reports of the investigations submitted within NDA 19-901.

Sincerely,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
EVP and Corporate Head, Regulatory Affairs

Cc: Ms. Tirtho Uppal, Cobalt Pharmaceuticals, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-021

Cobalt Pharmaceuticals Inc.
Attention: Ms. Tirth Uppal
6500 Kitimat Road
Mississauga, Ontario L5N 2B8
CANADA

Dear Ms. Uppal:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ramipril 1.25, 2.5, 5, and 10 mg Tablets
Review Priorty Classification:	Standard (S)
Date of Application:	January 10, 2006
Date of Receipt:	January 30, 2006
Our Reference Number:	NDA 22-021

Your January 10, 2006 submission was considered a 505(b)(2) fee paying human drug application. As such it was incomplete and was not accepted for consideration for filing because all fees owed for this application were not paid. Subsequently, we acknowledge receipt of your revised labeling on January 30, 2006. At that time, your application became a non-fee paying 505(b)(2) application, and the receipt date of the revised labeling is considered the new receipt date for this application.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

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 March 30, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 30, 2006.

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, Room 4160
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call:

Alisea Sermon, Pharm.D.
Regulatory Health Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

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

CC: James Parker, J.D., Ph.D.
U.S. Agent
Strategic Bioscience Corporation
93 Birch Hill Road
Stow, MA 01775
USA

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/s/

Edward Fromm
2/8/2006 09:21:21 AM

19 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

RHPM Overview of NDA 22-021
Altace (ramipril)
1.25, 2.5, 5 and 10 mg Tablets
February 28, 2007

Sponsor:	Cobalt Pharmaceuticals, Inc.
Application Date:	January 10, 2006
Receipt date:	January 30, 2006 (date removed from Arrears List)
User Fee Goal Date:	February 28, 2007

Background

Cobalt Pharmaceuticals submitted a non-fee paying, 505(b)(2) application for ramipril tablets on January 10, 2006. They believe that their product has been shown to be equivalent to the reference listed drug marketed by King Pharmaceuticals.

There was essentially only bioequivalence data in the application but upon review of the draft labeling for the NDA, it was determined that it was not identical to the RLD (Altace Capsules), and therefore was a fee paying application. The applicant submitted revised labeling on January 30, 2006 that was identical to the RLD; it was then removed from the Arrears List and January 30, 2006 became the new receipt date.

This NDA for ramipril tablets relies on the safety and efficacy findings of Altace Capsules (RLD) as well as the underlying raw data (see correspondence to FDA from King Pharmaceuticals dated March 3, 2006). This letter changed the status of the application from a 505(b)(2) application to a 505(b)(1); payment of ½ of a full user fee by the applicant is still outstanding and will be invoiced by the User Fee Staff.

The Agency received a letter dated September 22, 2006 from King Pharmaceuticals authorizing the use of the name Altace for the Cobalt Tablet application.

Medical

In his review dated February 8, 2007, Dr. Abraham Karkowsky recommended an approvable action for the use of Altace Tablets. Approval of this application is pending once an appropriate expiration date has been determined and a complete review of the drug substance from the new API (active pharmaceutical ingredient) supplier, ———————

Pharmacology Review

In his review dated May 9, 2006, Dr. Charles Resnick concluded that the application for Altace Tablets relies on the prior approval of King Pharmaceuticals NDA 19-901 for Altace capsules in lieu of providing non-clinical safety data. He stated that there are no differences between the two products in terms of proposed usage, and the prior Agency findings of safety and efficacy for the King Pharmaceuticals product serves as an acceptable substitute for toxicology studies of the Cobalt product.

Biopharmaceutical Review

In her review dated, August 15, 2006, Dr. Carol Noory finds the clinical pharmacology and Biopharmaceutics section of the proposed application acceptable. She noted that a waiver for the middle two strengths, 2.5 mg and 5.0 mg tablets was requested and found acceptable based on formulation

proportionality and similarity of the dissolution profiles using a single dissolution procedure to compare each strength to the 10 mg Ramipril lot used in the vivo studies. The sponsor's proposed dissolution specification, Q ——————————— is not acceptable. The following dissolution method and specification is recommended based on the data evaluated.

Statistical Review
N/A

Chemistry Review
In his review dated, August 26, 2006 and February 21, 2007, Dr. Prafull Shiromani recommended an approval action from a chemistry, manufacturing and controls perspective pending satisfactory recommendations from the Office of Compliance for facilities.

DSI
There were no clinical audits; bioequivalence audits were conducted and found to be acceptable (see DSI review dated November 22, 2006).

Pediatrics
The Division issued a pediatric waiver dated April 6, 2006 for the indication of hypertension; Dr. Stockbridge said that the other two indications in the labeling (reduction on the risk of myocardial infarction, stroke, and death from cardiovascular causes and heart failure post myocardial infarction) should also be granted full pediatric waivers.

DMETS
In a review dated February 15, 2007, DMETS noted that the name "ALTACE TABLETS" was acceptable.

Labeling
There are no outstanding labeling issues.

Advisory Committee Meeting
No meeting held.

RHPM Summary

A major CMC amendment was received on November 20, 2006, extending the review clock until February 28, 2007.

An approval on draft regulatory action will be drafted for Dr. Stockbridge's signature. SPL (Structured Product Labeling) will be requested in the approval letter.

Edward Fromm
Regulatory Health Project Manager