

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021951Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED UPON AND
AFTER APPROVAL OF AN NDA OR SUPPLEMENT**

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

NDA NUMBER

21-951

NAME OF APPLICANT/NDA HOLDER

Cipher Pharmaceuticals Inc.

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

TRADE NAME

ABSORICA™

ACTIVE INGREDIENT(S)

Isotretinoin

STRENGTH(S)

10, 20, 30, and 40 mg

DOSAGE FORM

Oral

APPROVAL DATE OF NDA OR SUPPLEMENT

05/25/2012

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions 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 approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

7,435,427

b. Issue Date of Patent

10/14/2008

c. Expiration Date of Patent

09/21/2021

d. Name of Patent Owner

Galephar M/F

Address (of Patent Owner)

Rue du Parc Industriel, 39

City/State

Marche en Famenne

ZIP Code

6900, Belgium

FAX Number (if available)

+32 84 32 04 53

Telephone Number

+32 84 32 04 52

E-Mail Address (if available)

bstre@galephar.be

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.)

Road 198 km 14.7 #100 Juncos Industrial Park

City/State

Juncos, Puerto Rico

ZIP Code

00777-3873

FAX Number (if available)

(787) 713-0344

Telephone Number

(787) 713-0340

E-Mail Address (if available)

adeboeck@galephar.com

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

Yes

No

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

Yes

No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. 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. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

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 approved NDA 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 NDA? 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 approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved 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

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes."
- the answer to 2.7 is "No."

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3? 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

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) | Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product? Yes No

4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)
--	--

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use 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 or supplement approved 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 06/05/2012
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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.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Jason A. Gross, Pharm. D.	
Address Cipher Pharmaceuticals Inc. 5650 Tomken Road, Unit 16	City/State Mississauga, Ontario
ZIP Code L4W 4P1	Telephone Number (905) 602-5840
FAX Number (if available) (301) 560-6640	E-Mail Address (if available) jgross@cipherpharma.com

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA 021951

SUPPL #

HFD # 540

Trade Name

Generic Name (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg, 40 mg

Applicant Name Cipher Pharmaceuticals Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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?

YES

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# 018662

Accutane (isotretinoin) Capsules, 10 mg, 20 mg, and 40 mg

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:

Investigation #1: Study ISOCT.08.01

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

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:

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"):

Investigation #1: Study ISOCT.08.01

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 # 64927 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
Explain:

! NO
! 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: Matthew White
Title: Regulatory Health Project Manager
Date: 5/4/2012

Name of Office/Division Director signing form: Susan J. Walker, MD, FAAD
Title: Director, Division of Dermatology and Dental Products

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/

MATTHEW E WHITE
05/23/2012

GORDANA DIGLISIC
05/23/2012

SUSAN J WALKER
05/25/2012

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-951 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: July 1, 2005 Action Date: May 1, 2006

HFD-540 Trade and generic names/dosage form: CIP -Isotretinoin Capsules

Applicant: Cipher Pharmaceuticals, Ltd. Therapeutic Class:

Indication(s) previously approved:

Each **approved** indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: severe recalcitrant nodular acne

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

Yes: Please proceed to Section A.

X 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:

Min birth kg _____ mo. _____ yr. _____ Tanner Stage _____
Max 11 years kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- X 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:

Min 12 kg _____ mo. _____ yr. _____ Tanner Stage _____
Max 17 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: Studies may have to be performed if the safety and/or efficacy profile of this drug product is different from Accutane.

Date studies are due (mm/dd/yy): N/A

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:

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}

Melinda Bauerlien, M.S.
Regulatory Project Manager

cc: NDA 21-951
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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

/s/

Melinda Harris-Bauerlien
4/26/2006 01:59:43 PM

Denise Cook
5/2/2006 01:59:03 PM

Jill Lindstrom
5/10/2006 04:51:05 PM

Stanka Kukich
5/11/2006 09:34:08 AM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 021951 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DDDP PDUFA Goal Date: 5/15/12 Stamp Date: 11/29/2011

Proprietary Name: _____

Established/Generic Name: Isotretinoin

Dosage Form: Capsules

Applicant/Sponsor: Cipher Pharmaceuticals

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For the treatment of severe recalcitrant nodular acne in patients 12 years of age and older

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

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

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below)

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

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 or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 6/2008)

Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992 (GDEA), requires that drug product applicants certify that they did not and will not use in any capacity the services of any debarred persons in connection with a drug product application. If the application is an abbreviated new drug application (ANDA), it must also include a list of all convictions described under section 306(a) and (b) of the Act (21 U.S.C. 335a(a) and (b)) that occurred within the previous 5 years and were committed by the applicant or affiliated persons responsible for the development or submission of the ANDA.

Cipher Pharmaceuticals Inc., 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.

Signed: 
Title: Vice President, Scientific and Medical Affairs
Date: November 21, 2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 021951 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Absorica Established/Proper Name: Isotretinoin Dosage Form: Capsules		Applicant: Cipher Pharmaceuticals Agent for Applicant (if applicable): Arthur M. Deboeck
RPM: Matthew White		Division: Division of Dermatology and Dental Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>NDA 018662 Accutane (isotretinoin) Capsules</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This application provides for a modified formulation and has different bioavailability under fasted conditions than the listed drug. Consequently, the capsules may be administered without regard to meals, whereas the listed drug is administered with meals.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 5/25/12</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
<p>❖ Actions</p> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>May 29, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists documents to be included in the Action Package.

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

<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None Approvable: 4/25/2007 Approvable: 5/1/2006
<ul style="list-style-type: none"> If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain. 	<input type="checkbox"/> Received
<ul style="list-style-type: none"> Application Characteristics³ <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Retinoid</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Communication Plan <input checked="" type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<ul style="list-style-type: none"> BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter) 	<input type="checkbox"/> Yes, dates
<ul style="list-style-type: none"> BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Public communications (<i>approvals only</i>) 	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	5/25/12
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval: 5/25/2012 Approvable: 4/25/2007 Approvable: 5/1/2006
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	5/25/12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	11/29/11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Accutane: January 2010

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	5/25/12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	11/29/11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	Amnesteem: February 2010
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	5/25/12
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	Proprietary Name Denied (submitted to IND 64927): 12/13/11 Proprietary Name Denied: 4/3/12 Proprietary Name Accepted: 5/18/12 Review: 12/13/11 Review: 4/3/12 Review: 5/17/12 Review: 5/18/12
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 2/3/12 <input checked="" type="checkbox"/> DMEPA 3/23/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) DMPP: 4/30/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 5/8/12 <input checked="" type="checkbox"/> SEALD 5/21/12 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM Filing Review: 12/28/2005 Memo of Filing Meeting: 1/3/2006 <input type="checkbox"/> Not a (b)(2) Cleared on 4/9/12 <input type="checkbox"/> Not a (b)(2) 4/26/12
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Application does not trigger PREA because it is not a new active ingredient, indication, dosage form, dosing regimen or rout of administration</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) 	Labeling Comments: 5/18/12 Labeling Comments: 5/9/12 Labeling Comments: 5/4/12 PMC: 4/27/12 Labeling Comments: 4/12/12 IR: 4/10/12 Safety Update Request: 4/5/12 IR: 4/4/12 IR: 4/2/12 IR: 3/14/12 Labeling Comments: 3/5/12 IR: 2/17/12 IR: 2/9/12 IR: 1/12/12 Ack Class 2 Resub: 12/13/11 IR: 12/7/11 IR: 9/15/11 Ack PropName Withdraw: 7/18/11 Advice: 6/4/08 Advice: 10/25/07 Dispute Appeal Response: 8/10/07 Dispute Appeal Meeting: 7/5/07 Ack Dispute Appeal: 6/4/07 IR: 3/21/07 IR: 3/6/07 IR: 2/12/07 IR: 1/24/06 IR: 12/8/05 IR: 11/14/05 Filing Issues Identified: 10/26/05 Advice: 10/4/05 Ack NDA: 7/12/05
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg 6/27/2007
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	Guidance: 8/6/2008 Guidance: 1/28/2008 Stalled Development: 10/1/2007 Dispute Resolution: 7/11/2007

	Guidance Meeting: 3/13/2006
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/25/12 Previous Review Cycles: 4/27/07
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/8/12 Previous Review Cycles: 4/19/07 4/27/06
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1: 4/27/12
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	4/23/12 Previous Review Cycles: 4/19/07 4/27/06
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	4/23/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None MHT: 5/10/12 DRUP: 4/10/12 Ophthalmology: 2/21/12 and 4/9/12 Psychiatry: 2/27/12 Audiology: 2/29/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	REMS Document: 4/25/12 REMS Notification Letter: 4/12/12 DRISK REMS review: 5/10/12 REMS Document not included with REMS Notification Letter or DRISK Review in the action package. Refer to 4/25/12 REMS document submission. <input type="checkbox"/> None
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	

⁶ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/4/12
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None Cetero response Review: 5/4/12 Discipline Review: 4/12/12 Previous Review Cycles: 4/9/07 4/21/06 4/19/06
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 4/10/12 Previous Review Cycles: 4/25/07 4/18/06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 4/18/12 Addendum: 5/21/12 Previous Review Cycles: 4/12/07 4/13/06
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None Biopharmaceutics: Addendum: 5/7/12 Review: 4/16/12
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		4/12/07
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: 5/21/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



NDA 021951

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Cipher Pharmaceuticals Inc.
c/o Galephar P.R. Inc.
Road 198 km 14.7 #100 Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

ATTENTION: Arthur M. Deboeck, U.S. Agent
Vice President and General Manager, Galephar P.R. Inc.

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) dated June 27, 2005, received July 1, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isotretinoin Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We also refer to your correspondence dated and received April 16, 2012, requesting review of your proposed proprietary name, Absorica. We have completed our review of the proposed proprietary name, Absorica and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your April 16, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew White at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
05/18/2012

From: White, Matthew
Sent: Friday, May 04, 2012 12:35 PM
To: 'Julia Chan'
Cc: Gould, Barbara
Subject: NDA 021951 for (isotretinoin) Capsules: Carton/Container Labeling
Ms. Chan,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We also refer to your April 26, 2012 submission, containing draft labeling.

We have reviewed your draft carton and container labeling and have the following comments. Please resubmit draft carton and container labeling with the following comments addressed or your counterproposal by May 11, 2012.

Blister Labels and Carton Labeling, 10 mg, 20 mg, 30 mg and 40 mg

1. Revise the presentation of the proprietary name, ABSORICA, from UPPERCASE to Title Case "Absorica" to improve readability of the name.
2. Revise storage conditions to "STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) [SEE USP CONTROLLED ROOM TEMPERATURE]. PROTECT FROM LIGHT."

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: matthew.white@fda.hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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

/s/

MATTHEW E WHITE

05/14/2012

Emailed to the sponsor on 5/4/12

REV-CLINPHARM-02 (Review Noted (NAI))
NDA-021951
ORIG-1
Supporting Document 31
Clinical/Response To Information Request
Submit Date: 10/12/2011 - FDA Received Date: 10/12/2011

In response to the FDA Information Request dated September 15, 2011, Cipher Pharmaceuticals, Inc. confirmed that there were no studies conducted by Cetero Research in Houston, Texas during the period of concern (April 1, 2005 to June 15, 2010) submitted to NDA 21-951.

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

/s/

CHINMAY SHUKLA
05/04/2012

DOANH C TRAN
05/04/2012

From: White, Matthew
Sent: Friday, April 27, 2012 1:42 PM
To: 'Julia Chan'
Cc: Gould, Barbara
Subject: PMC for NDA 021951 (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg, 40 mg
Dear Ms. Chan,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (CIP-isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We also refer to your November 29, 2011 submission, containing a complete response to the NDA Approvable Letter dated April 25, 2007.

As communicated in an email dated April 11, 2012 and agreed to in an amendment dated April 18, 2012, the Agency has identified the following postmarketing commitment study to be conducted post approval:

PMC #1 Description: Dissolution method development study

Conduct an *in vitro* dissolution method development study to define final test method parameters for quality control. Evaluate the utility of a two-tiered dissolution method (e.g., USP dissolution test 1 for isotretinoin capsules), identify different parameters that allow for enzyme use in accordance with USP guidelines, and identify a suitable surfactant that can be used at lower concentrations, ideally <2%. Other test method parameters may be evaluated, as desired, to assure the development of a robust dissolution test in line with the principles of USP <711> and <1092>. The optimal dissolution test method for your isotretinoin capsules should allow for reproducible product profiles (RSDs <10%).

FDA will make a decision on the final dissolution method for your isotretinoin capsules after reviewing your dissolution method report. Once an agreement is reached on the final test method, use the final test method to propose final dissolution acceptance criteria for your isotretinoin capsules. Your proposal should be supported by dissolution data from at least the first three (3) validation-lots of each capsule strength, and two (2) additional commercial batches of each strength. If the dissolution report provides for a new faster-release dissolution method (i.e., complete release/dissolution for all the strengths in < 90 minutes) and the provided data support the approval of this method, you may propose the implementation of a single-point dissolution criterion. Otherwise, implement at least a two-point criteria, with the first time point being a range of appropriate variability (ideally +/- 10%).

PMC Schedule Milestones: Final Protocol Submission Date:
Study Completion Date:
Final Report Submission Date: 11/29/2012

Please submit to your NDA by Tuesday, May 1, 2012 your agreement to conduct the study above and your timeline for final protocol submission and study completion.

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: matthew.white@fda.hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
04/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Cipher Pharmaceuticals Inc.

DATE OF SUBMISSION

04/25/2012

TELEPHONE NO. (Include Area Code)

(905) 602-5840

FACSIMILE (FAX) Number (Include Area Code)

(301) 560-6640

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

5650 Tomken Road, Unit 16
Mississauga
Ontario L4W 4P1
Canada

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

Arthur M. Deboeck

Galephar P.R. Inc., Road 198 km 14.7 #100 Juncos Industrial Park,
Juncos 00777-3873, Puerto Rico. Tel: (787) 713-034 Fax: (787)713-0344

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 021951

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Isotretinoin, USP

PROPRIETARY NAME (trade name) IF ANY

ABSORICA™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

N/A

CODE NAME (if any)

N/A

DOSAGE FORM:

Capsules

STRENGTHS:

10, 20, 30 and 40 mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE:

Severe recalcitrant nodular acne

APPLICATION DESCRIPTION

APPLICATION TYPE

(check one)

- NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

- 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug ACCUTANE® (isotretinoin) CAPSULES Holder of Approved Application Hoffmann-La Roche Inc

TYPE OF SUBMISSION (check one)

- ORIGINAL APPLICATION AMENDMENT TO APENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

- CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED REMS for NDA 021951 (SEQ-0016)

PROPOSED MARKETING STATUS (check one)

- PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

N/A

THIS APPLICATION IS

- PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attachment providing Establishment Information.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Not applicable.

This application contains the following items: (Check all that apply)	
<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) _____

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Arthur M. Deboeck, VP & Gen Mgr, Galephar PR	04/25/2012
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
US Agent, Galephar PR Inc., Juncos, Puerto Rico, 00777-3873		(787)713-0340

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448
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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.

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. applicant should be entered in the indicated area. Only one person should sign the form.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing, and Controls Supplement = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

Submission of Partial Application Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

CBE "Supplement-Changes Being Effected" supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

CBE-30 "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

Prior Approval (PA) "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is

Paper Paper and Electronic Electronic

Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File (DMF) number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, Investigational New Drug Applications (INDs), NDAs, Premarket Approval Applications (PMAs), Premarket Notifications (510(k)s), Investigational Device Exemptions (IDEs), Biological Master Files (BMFs) and DMFs that are referenced in the current application.

Items 1 through 20 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

From: White, Matthew

Sent: Thursday, April 12, 2012 3:32 PM

To: 'Julia Chan'

Cc: Gould, Barbara

Subject: NDA 021951 for (isotretinoin) Capsules: Carton and Container Labeling

Dear Ms. Chan,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We also refer to your February 3, 2012 submission, containing draft labeling.

We have reviewed your draft carton and container labeling and have the following comments. Please resubmit draft carton and container labeling with the following comments addressed or your counterproposal by April 18, 2012.

A. Blister Labels and Carton Labeling, 10 mg, 20 mg, 30 mg and 40 mg

1. Please remove all references to the phrase [REDACTED] (b) (4) from the labels and labeling. This product was found to be an immediate release [REDACTED] (b) (4)
2. The drug name needs to be revised to "(isotretinoin) Capsules".
3. Add the following statement at the top of your principal display panel where the company name is presently per 21 CFR 208.24(d): [REDACTED] Attention Pharmacist: Dispense with enclosed Medication Guide [REDACTED] .
4. Your principal display panel is extremely crowded. To reduce clutter and allow room for the medication guide statement, we request you delete the company name on the principal display panel. This information is redundant and detracts from other important information such as the proprietary and established names and strength.
5. Ensure the established name is at least ½ size of proprietary name and has a commensurate prominence with proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. See 21 CFR 201.10(g)(2).

B. Blister Labels, 10 mg, 20 mg, 30 mg, and 40 mg

1. Ensure the strength statement follows the proprietary and established names. Currently, the side panels and the lower right portion of the principal display panel only display the strength.
2. Decrease the size of the [REDACTED] Rx only [REDACTED] statement and relocate to the bottom of the principal display panel. As presented, it detracts from important information such as the strength.

3. Decrease the size of the statement " 10 capsules prescription pack" . As presented, it detracts from the proprietary and established names as well as the strength.

C. Carton Labeling, 10 mg, 20 mg, 30 mg, and 40 mg

1. Decrease the size of the statement " 30 capsules" . As presented, it detracts from the proprietary and established names as well as the strength.

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: matthew.white@fda.hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
04/12/2012

McKnight, Rebecca

From: McKnight, Rebecca
Sent: Thursday, April 05, 2012 6:19 PM
To: Hughes, Minerva; White, Matthew
Subject: Fw: Cipher NDA 21-951 - CMC Response

Importance: High

Attachments: Dissolution Acceptance Criteria.pdf



Dissolution
Acceptance Criteri...

----- Original Message -----

From: Julia Chan [mailto:jchan@cipherpharma.com]
Sent: Thursday, April 05, 2012 04:37 PM
To: McKnight, Rebecca
Subject: RE: Cipher NDA 21-951 - CMC Response

Hi Becky,

In response to the FDA's comments below, please refer to the attached report entitled Dissolution Acceptance Criteria.

Cipher would also like to provide clarification with respect to the FDA comment in item 2, "...the lack of dose proportionality across all strengths". Cipher has conducted in vivo dose proportionality studies, which were submitted to the Agency on October 26, 2006, in response to a question in the May 1, 2006, approvable letter. Subsequent correspondence received by Cipher indicated that dose proportionality had been demonstrated, and the issue resolved.

Further dose proportionality studies, concerning the more recently developed 40 mg dosage strength, ISOPK.09.01 and ISOPK.09.02, were submitted in the NDA Amendments on November 4, 2010, and December 12, 2011 (Seq 0001).

Cipher trusts that our refined dissolution specifications, along with our commitment to reevaluate these specifications after additional data is obtained, is in line with FDA's expectations. However, we welcome open dialogue with the FDA to resolve any concerns or provide further clarification.

This response will be part of a consolidated formal amendment scheduled for April 12, 2012.

Kind regards,
Julia

Julia Chan, RAC
Associate Director, Regulatory Affairs
Cipher Pharmaceuticals Inc.
5650 Tomken Road, Unit 16
Mississauga, ON
L4W 4P1

Tel: 905 602 5840 ext 326
Fax: 905 602 0628
jchan@cipherpharma.com

CONFIDENTIALITY NOTICE - This e-mail transmission, and any documents, files or previous e-mail messages attached to it may contain information that is confidential or legally privileged. If you are not the intended recipient, or a person responsible for delivering it to the intended recipient, you are hereby notified that you must not read this transmission and that any disclosure, copying, printing, distribution or use of any of the information contained in or attached to this transmission is STRICTLY PROHIBITED. If you have received this transmission in error, please immediately notify the sender by telephone or return e-mail and delete the original transmission and its attachments without reading or saving in any manner. Thank you.

-----Original Message-----

From: McKnight, Rebecca [mailto:Rebecca.McKnight@fda.hhs.gov]
Sent: April 4, 2012 10:59 AM
To: Julia Chan
Subject: RE: Cipher NDA 21-951 - CMC Response
Importance: High

Hi Julia,

Please address the following items:

- (1) In your response to FDA's recommended dissolution acceptance criteria, you stated that the proposed multi-point acceptance limits would result in failures for clinical lots. Please specify the lot numbers and provide the associated dissolution profile data (mean, individuals, and RSDs) for review. Please note that a dissolution failure means that the lot would fail at stage 3 testing as per USP.
- (2) During the 29 March 2012, FDA believed that we reached an agreement with Cipher that a single acceptance limit was not appropriate for all capsule strengths given the differences in drug release profiles for each strength, the lack of bioequivalence to the listed drug under fasting conditions, and the lack of dose proportionality across all strengths. Your proposed dissolution acceptance limits are unclear in the 3 April 2012 information amendment. Please provide your proposed dissolution acceptance limits for each capsule strength. The dissolution acceptance criteria should be based on the available dissolution data, in accordance with FDA guidelines.

Please provide responses to these items by 4pm today, April 4, 2012.

Thank you.

Rebecca McKnight
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
Food and Drug Administration
(301) 796-1765

McKnight, Rebecca

From: McKnight, Rebecca
Sent: Thursday, April 05, 2012 12:23 PM
To: 'Julia Chan'
Subject: RE: Cipher NDA 21-951 - CMC Response

Hi Julia,

Please respond to the additional CMC question below by COB tomorrow, April 6, 2012:

-Please resubmit the comparison figure 3 (page 24) using correct data points (there are no 24 months results) for 40mg capsules at long term condition in stability report Study ST046.

Please submit via email and as an amendment to your application.

Thank you.

Rebecca McKnight
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
Food and Drug Administration
(301) 796-1765

McKnight, Rebecca

From: McKnight, Rebecca
Sent: Tuesday, April 03, 2012 12:47 PM
To: 'Julia Chan'
Subject: RE: T-con items

Hi Julia,

Please let me know when you plan on submitting the information listed below. The information requested is important in order for us to continue the review of your application.

In addition to the points mentioned below, during the 03/29/12 teleconference, Cipher accepted the Agency's recommendation to implement a different dissolution specification for each strength; however, an alternate proposal on tolerance limits will be made after Cipher reviews the available data. Please provide the proposed dissolution specification for review, with appropriate justification as soon as possible.

Thanks,
Becky

-----Original Message-----

From: Julia Chan [mailto:jchan@cipherpharma.com]
Sent: Thursday, March 29, 2012 3:56 PM
To: McKnight, Rebecca
Cc: White, Matthew
Subject: RE: T-con items

Hi Becky,

Thank you again for the teleconference this morning, concerning NDA 21-951, which seemed to be very productive. To reiterate the action items covered at the end of the call:

- Regarding CMC Comment (3), Cipher will submit the 18 month interim stability report tomorrow, March 30, 2012, via email.
- Regarding ONDQA-Biopharmaceutics Comments (1) and (2), Cipher plans to submit responses on Monday, April 2, 2012, via email.
- The consolidated formal submission containing responses to the above mentioned comments, will be submitted as soon as possible after April 2, 2012, by April 6, 2012, at the latest. Please confirm that this is acceptable.

Our attendees on today's call were as follows:

Jason A. Gross, Pharm D, VP Scientific Affairs, Cipher Pharmaceuticals Inc.
Julia Chan, Associate Director, Regulatory Affairs, Cipher Pharmaceuticals Inc.
Arthur Deboeck, VP and General Manager, Galephar Pharmaceutical Research, Inc.
Scott Tomsky, Sr. Director, Regulatory Affairs, Ranbaxy Laboratories, Inc.

Kind regards,
Julia

-----Original Message-----

From: Julia Chan
Sent: March 29, 2012 8:45 AM
To: 'McKnight, Rebecca'
Subject: RE: T-con items

Hi Becky,

Thank you very much for providing this further information. We look forward to the discussion at 10am.

Kind regards,
Julia

-----Original Message-----

From: McKnight, Rebecca [mailto:Rebecca.McKnight@fda.hhs.gov]
Sent: March 29, 2012 8:09 AM
To: Julia Chan
Subject: T-con items

Hi Julia,

To facilitate the discussion, please consider the following:

CMC

(1) Established name needs to be revised to:
Brand name (isotretinoin) Capsules

(2) The current NDC numbers [REDACTED] (b) (4)

[REDACTED] (b) (4) The numbers should reflect the to-be-marketed products.

(3) The available stability data do not support the proposed expiration dating period for the 40 mg strength capsules. Only [REDACTED] (b) (4) is granted for the 40 mg capsules.

ONDQA-Biopharmaceutics

(1) Additional clarification/justification is needed to support the following dissolution method parameters:

[REDACTED] (b) (4)

(2) A multi-point specification is recommended for quality control, as per FDA Guidance - Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Recommended acceptance criteria are as follows:

[REDACTED] (b) (4)

Thanks,

Becky

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

/s/

REBECCA A MCKNIGHT
04/10/2012

From: Ding, Shulin
Sent: Wednesday, April 04, 2012 4:15 PM
To: Mehta, Tarun; Rhee, Moo Jhong
Cc: Diglisic, Gordana; White, Matthew; Brown, Patricia C (ODEIII)
Subject: FW: NDA 21-951 Isotretinoin Capsules < Biopharmaceutics Information Request - Urgent>

From: Hughes, Minerva
Sent: Wednesday, April 04, 2012 3:47 PM
To: Ding, Shulin
Subject: FW: NDA 21-951 Isotretinoin Capsules < Biopharmaceutics Information Request - Urgent>

Hello Shulin,

Biopharmaceutics interactive comments conveyed to the Applicant today are summarized below for your reference. We will continue to work interactively and quickly with the Applicant to resolve the outstanding issues.

Thanks,
Minerva

From: McKnight, Rebecca
Sent: Wednesday, April 04, 2012 11:00 AM
To: Hughes, Minerva; Tran-Zwanetz, Catherine; White, Matthew
Cc: Dorantes, Angelica
Subject: RE: NDA 21-951 Isotretinoin Capsules < Biopharmaceutics Information Request - Urgent>

Hello,

These responses were just sent to Cipher. I will forward the responses as soon as I receive them.

Thanks,
Becky

From: Hughes, Minerva
Sent: Wednesday, April 04, 2012 10:46 AM
To: McKnight, Rebecca; Tran-Zwanetz, Catherine; White, Matthew
Cc: Dorantes, Angelica
Subject: NDA 21-951 Isotretinoin Capsules < Biopharmaceutics Information Request - Urgent>
Importance: High

Hello,

Please convey the following ONDQA-Biopharmaceutics information request to the Applicant this morning (i.e., as soon as possible), and request responses by close of business today, 4 April 2012.

(1) In your response to FDA's recommended dissolution acceptance criteria, you stated that the proposed multi-point acceptance limits would result in failures for clinical lots. Please specify the lot numbers and provide the associated dissolution profile data

(mean, individuals, and RSDs) for review. Please note that a dissolution failure means that the lot would fail at stage 3 testing as per USP.

(2) During the 29 March 2012, FDA believed that we reached an agreement with Cipher that a single acceptance limit was not appropriate for all capsule strengths given the differences in drug release profiles for each strength, the lack of bioequivalence to the listed drug under fasting conditions, and the lack of dose proportionality across all strengths. Your proposed dissolution acceptance limits are unclear in the 3 April 2012 information amendment. Please provide your proposed dissolution acceptance limits for each capsule strength. The dissolution acceptance criteria should be based on the available dissolution data, in accordance with FDA guidelines.

Thanks,

Minerva

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/s/

MATTHEW E WHITE
04/05/2012

From: White, Matthew

Sent: Thursday, April 05, 2012 2:20 PM

To: 'Julia Chan'

Cc: Gould, Barbara

Subject: Safety Update for NDA 021951 (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg, and 40 mg

Ms. Chan,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We also refer to your November 29, 2011 submission, containing a complete response to the NDA Approvable Letter dated April 25, 2007.

The safety update for this application, as described at 21 CFR 314.50(d)(5)(vi)(b), is overdue. Please submit the safety update by COB Friday, April 6, 2012. The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - o Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - o Present tabulations of the new safety data combined with the original NDA data.
 - o Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - o For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration

E-mail: matthew.white@fda.hhs.gov

Phone: 301-796-4997

Fax: 301-796-9895

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/s/

MATTHEW E WHITE
04/05/2012



NDA 021951

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Cipher Pharmaceuticals Inc.
c/o Galephar P.R. Inc, U.S. Agent
Road 198 km 14.7 #100, Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

ATTENTION: Arthur M. Deboeck
Vice President and General Manager, Galephar P.R. Inc.

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) dated June 27, 2005, received July 1, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isotretinoin Capsules, 10 mg, 20 mg, 30 mg, and 40 mg.

We also refer to your January 4, 2012 correspondence, received January 5, 2012, requesting review of your proposed proprietary name, (b) (4), and to your correspondence dated and received February 3, 2012, amending your proprietary name submission. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill, covering the majority of the lower half of the page.

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

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew White at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/03/2012

From: White, Matthew
Sent: Monday, April 02, 2012 3:30 PM
To: 'Julia Chan'
Cc: Gould, Barbara
Subject: Request for Information: NDA 021951 for (isotretinoin) Capsules

Importance: High
Ms Chan,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We have the following information request for which we request an email response by COB today, April 2, 2012. Please follow up your email response with formal submission to the NDA.

Provide the normal range for the following serum laboratory parameters that were obtained in clinical trial ISOCT.08.01:

- Total cholesterol
- HDL cholesterol
- LDL cholesterol
- Triglycerides
- CK (creatine kinase)
- Glucose

Please contact me if you have any questions.

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: matthew.white@fda.hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
04/02/2012



NDA 021951

INFORMATION REQUEST

Cipher Pharmaceuticals Inc.
c/o Galephar P.R. Inc, U.S. Agent
ATTENTION: Arthur M. Deboeck
Vice President and General Manager, Galephar P.R. Inc.
Road 198 km 14.7 #100, Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We also refer to your November 29, 2011 submission, containing a complete response to the NDA Approvable Letter dated April 25, 2007.

We have the following information request for which we request a prompt written response by March 20, 2012 in order to continue our evaluation of your NDA.

- Verify if the Batch/ Lot Numbers used in the following clinical trials were to-be-marketed formulations and identify where in the submission these Batch/Lot numbers, described under the CMC section, are located.
 1. Batch/Lot Number: IJ08 used in trial ISOPK.08.02
 2. Batch/Lot Number: 5D102 and 5D103 used in trials ISOPK.09.01 and ISOPK.09.02

If you have any questions, call Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BARBARA J GOULD

03/14/2012

qq DIVISION DIRECTOR Susan Walker



NDA 021951

INFORMATION REQUEST

Cipher Pharmaceuticals Inc.
c/o Galephar P.R. Inc, U.S. Agent
ATTENTION: Arthur M. Deboeck
Vice President and General Manager, Galephar P.R. Inc.
Road 198 km 14.7 #100, Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (CIP-isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We also refer to your November 29, 2011 submission, containing a complete response to the NDA Approvable Letter dated April 25, 2007.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a written response by Friday, February 24, 2012 in order to continue our evaluation of your NDA.

Chemistry, Manufacturing and Controls

Drug Substance:

1. Provide the particle size distribution data for the drug substance lots used in the manufacture of clinical batches 000452, 000482, 000537 and 000453, and the drug substance lots manufactured at (b) (4) site.
2. To qualify (b) (4) site as an alternative drug substance site, provide comparative dissolution study results for each strength of capsules manufactured using the drug substance from the original site and the alternative site. The study should be conducted using the proposed regulatory method, and the samples should be pulled hourly for at least four hours. For each drug substance site, 12 capsules from one drug product batch per strength should be studied. Capsules from clinical batches are preferred if feasible.

Ophthalmologic Assessment

1. The analyses provided in the Clinical Study Report (CSR) relating to visual acuity and adverse events (ocular) are not correctly performed.
 - a. Visual acuity assessed on the Snellen Eye Chart is reported as a “line shift” away/towards 20/20. This is incorrect because 20/20 is not the best vision that can be achieved. Some line shifts from 20/20 represent improvement in visual acuity and some line shifts represent an impairment of visual acuity. It is important to count improvement in visual acuity as an improvement and distinguish it from a worsening of vision.

Snellen Visual acuity is best analyzed by conversion to logMAR, then reporting -0.3, -0.2, -0.1, 0, 0.1, 0.2, 0.3 and >0.3 log changes. The Snellen acuity for each subject on each visit is recorded so it should be converted and analyzed.

- b. When data listings are reviewed, there are numerous instances where decreased vision under dim light condition is coded as “visual acuity reduced.” This inaccurately captures the number of reported cases of both visual acuity reduction and night blindness. In addition, as an adverse event, it is not clear how Xerophthalmia is being distinguished from Dry Eye or how conjunctival hyperemia is being distinguished from conjunctivitis. The incidence of eye events should be recalculated.
 - c. The protocol states that patients who present with issues requiring a full ophthalmic work-up will be referred to the patient’s own or a local ophthalmologist recommended by the investigator for further evaluation. Patients presenting with night blindness will have an electroretinogram (ERG) performed as a part of the diagnostic workup for the night blindness.

Two subjects in the CIP-isotretinoin group discontinued due to eye events (night blindness; punctate keratitis), but there is no discussion or analysis within the study report indicating the number of subjects requiring a full ophthalmic workup or what was found during the full ophthalmic workup. This information should be provided. If only two subjects were referred for full evaluation, there should be an explanation why patients were referred for evaluation, but the evaluation was not analyzed.

The CSR states that follow-up reports of available [ophthalmic] evaluations were included in the patient’s study record. This information does not appear to be present in Appendix 16.3.1 for subjects 23/004 and 43/002. The exact location of the follow-up reports of available ophthalmic evaluations for these subjects should be provided.

Bone Mineral Density

1. The dataset for bone mineral density does not include values for bone mineral content or area, from which bone mineral density results are calculated. Provide an updated dataset that includes values for bone mineral content and bone area. Include a variable that indicates whether a pediatric scan mode was utilized. Also include the version of the scanning

software that was used at the time of the scan. This information should be readily available from your DXA coordination center.

2. Provide information regarding the instructions, training, instrument quality control and cross calibration methods used
3. Provide the short-term precision testing using the [REDACTED] ^{(b) (4)} which was measured 10x on each machine at all investigative sites.
4. As outlined in the FDA letter dated February 1, 2010, we requested that you conduct total body less head (TBLH) measurements for adolescents at clinical sites where this measure is available. Provide the data or justify why this data was not collected.
5. As outlined in the FDA letter dated February 1, 2010, we recommend follow-up BMD until return to baseline or for up to 12 months of any adolescent (age 12-17) subject who sustains $\geq 4\%$ BMD decline at lumbar spine or total hip, or $\geq 5\%$ BMD decline at the femoral neck, or who has a final Z-score of < -2 at any site.

Based on the sparse follow-up data provided in the submission, recovery of bone density after cessation of study drug does not occur. Provide the follow-up bone mineral density data requested or justify why it was not collected.

If you have any questions, call Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GORDANA DIGLISIC
02/17/2012

From: White, Matthew
Sent: Thursday, February 09, 2012 12:00 PM
To: 'Julia Chan'
Cc: Gould, Barbara
Subject: NDA 021951 for CIP-isotretinoin Capsules, 10, 20, 30 and 40 mg

Dear Ms. Chan

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (CIP-isotretinoin) Capsules, 10, 20, 30 and 40 mg.

We also refer to your November 29, 2011 submission containing your response to the April 25, 2007 approvable letter.

We have the following request for information:

- For Studies ISOPK.09.01 and ISOPK.09.02, provide long term stability data for the internal standard isotretinoin ¹³C₃ to demonstrate that the internal standard was stable for the entire duration of pharmacokinetic sample bioanalysis.

Please provide the requested information no later than Monday, February 12, 2012.

Regards,

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: matthew.white@fda.hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
02/09/2012



NDA 021951

INFORMATION REQUEST

Cipher Pharmaceuticals Inc.
c/o Galephar P.R. Inc, U.S. Agent
ATTENTION: Arthur M. Deboeck
Vice President and General Manager, Galephar P.R. Inc.
Road 198 km 14.7 #100, Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (CIP-isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We also refer to your November 29, 2011 submission, containing a complete response to the NDA Approvable Letter dated April 25, 2007.

We are reviewing the Quality section of your submission and have the following information requests. We request a written response by January 27, 2012, in order to continue our evaluation of your NDA.

Biopharmaceutics

We acknowledge your response to deficiency #2 in the April 25, 2007, NDA Approvable Letter concerning the dosage form and dissolution method and request that you provide the following additional information to support your claims.

1. The solubility and stability profile of the drug substance over the pH range of 1 – 8.0. Please note that that solution pH should be evaluated before and after the test.
2. A complete dissolution method development report containing details on the testing performed to select the optimal parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, sinkers, etc.). The type and amount of any additives (enzymes, surfactants, etc.) should be justified with data. We recommend the use of at least twelve samples per testing variable, and include the complete dissolution data (individual, mean, SD, profiles) for your product in the report.
3. Please note that comparing the dissolution profiles for your product with another marketed product using the proposed dissolution method is not sufficient to demonstrate the discriminating capabilities of your method as per USP <1092>. Provide a summary

of the testing completed to establish that your proposed dissolution method can detect changes in composition or manufacturing process outside the operational ranges that might be expected to affect clinical performance. Your drug product formulation includes the multifunctional excipient (b) (4), (b) (4). Therefore, we recommend that your evaluation of the method's discriminating capabilities include information on the method's ability to detect and reject product manufactured with abnormal levels of drug, (b) (4) and soybean oil, and non validated mixing times and process temperatures. Provide the complete dissolution data (individual, mean, SD, profiles) for all variables tested.

4. To better understand the mechanistic basis for the observed differences in dissolution profile characteristics between your proposed product and approved isotretinoin drug products, please provide comparative dissolution profile data for at least one of listed products referenced in your application using the USP monograph dissolution method for that product. Refer to the approved product's labeling for information on which USP test the product complies with.
5. As noted in a previous comment, the FDA considers the excipient (b) (4) to have (b) (4) properties when formulated with lipophilic drug substances such as isotretinoin based on the available scientific literature. Please provide your scientific rationale as to why it is not appropriate to view the excipient (b) (4) agent in your formulation. We recommend that you provide copies of any scientific literature used to support your position.
6. To support your proposed specification time and limit, please provide all available dissolution profile data (i.e., multi-point sampling) for the clinical and registration lots at release and on stability. This information will also be used to support setting an expiration dating period for your product.
7. Provide comparative in vitro dissolution data to support the change in capsule shell color for the 20 mg, 30 mg, and 40 mg strengths. Complete dissolution data (individual, mean, RSD, and profiles), with adequate sampling (i.e., 15, 30, 45, 60, 120 minutes etc) until either (b) (4) of the drug is released or an asymptote is reached, using at least 12 samples for the changed and unchanged product is requested. For Similarity f2 testing, the reference product should be the unchanged product.

Please note that we are unable to complete our review of your claims in the absence of the requested information. If the requested information was provided under a previous NDA amendment, we request that you resubmit this information to the Complete Response submission in eCTD format, so that all pertinent information is consolidated in one location.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of the response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Matthew White, Regulatory Project Manager the Office of New Drugs (Matthew.White@fda.hhs.gov).

If you have any questions regarding this letter, call Jeannie David at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
01/12/2012
Chief, Branch IV



IND 064927

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Cipher Pharmaceuticals Inc.
c/o U.S. Agent: Galephar PR Inc.
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

ATTENTION: Arthur M. Deboeck
U.S. Agent

Dear Mr. Deboeck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Isotretinoin Capsules, 10 mg, 20 mg, 30 mg, and 40 mg.

We also refer to:

- your June 15, 2011, correspondence, received June 16, 2011, requesting review of your proposed proprietary name, (b) (4).
- the December 5, 2011, teleconference with DMEPA discussing the unacceptability of the proposed name (b) (4).
- and your December 6, 2011, e-mail correspondence to DMEPA providing rationale in support of the proposed name.

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew White at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/13/2011



NDA 021951

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Cipher Pharmaceuticals Inc.
c/o Galephar P.R. Inc
ATTENTION: Arthur M. Deboeck
Vice President and General Manager, Galephar P.R. Inc.
Road 198 km 14.7 #100, Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

Dear Mr. Deboeck:

We acknowledge receipt on November 29, 2011 of your November 28, 2011 resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (CIP-isotretinoin) Capsules, 10 mg, 20 mg, 30 mg and 40 mg.

We consider this a complete, class 2 response to our April 25, 2007 action letter. Therefore, the user fee goal date is May 29, 2012.

If you have any questions, call me at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Matthew White
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MATTHEW E WHITE
12/13/2011

October 12, 2011

RECEIVED

OCT 13 2011

CDR

Susan Walker, M.D.
Division Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg 22 Rm 5168
Silver Spring, MD 20993

ORIGINAL

80-31

Re: **NDA 21-951**
CIP-ISOTRETINOIN CAPSULES 10 mg, 20 mg, 30 mg and 40 mg
Response to September 15, 2011, Information Request – Cetero Research

Dear Dr. Parks:

Reference is made to Cipher Pharmaceuticals Inc.'s New Drug Application (NDA) 21-951 for CIP-ISOTRETINOIN Capsules, 10 mg, 20 mg, 30 mg and 40 mg, which is currently pending. Further reference is made to the Division's September 15, 2011 Information Request letter, concerning Cetero Research, in Houston, Texas (a copy of which is provided for ease of reference).

FDA Request:

The September 15, 2011, FDA correspondence requests that Cipher inform the FDA if we have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010).

Cipher Response:

In response to the above noted request, Cipher hereby confirms that no studies submitted to NDA 21-951 for CIP-ISOTRETINOIN CAPSULES, have been conducted by Cetero Research in Houston, Texas.

The original and two (2) copies of this correspondence are provided, each consisting of one volume. In addition, a desk copy of this submission is being provided to the Office of New Drugs, as requested in the attached letter.

Should you have any questions, please do not hesitate to contact our Associate Director of Regulatory Affairs, Ms. Julia Chan. She may be contacted by telephone at 905 602 5840 extension 326, or by e-mail at jchan@cipherpharma.com.

Yours sincerely,

A handwritten signature in black ink, appearing to read "J. Gross".

for
Jason A. Gross, Pharm.D.
Vice President, Scientific and Medical Affairs
Cipher Pharmaceuticals Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Cipher Pharmaceuticals Inc.	DATE OF SUBMISSION 10/12/2011
TELEPHONE NO. (Include Area Code) (905) 602-5840	FACSIMILE (FAX) Number (Include Area Code) (301) 560-6640
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 5650 Tomken Road, Unit 16 Mississauga Ontario L4W 4P1 Canada	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Arthur M. Deboeck Galephar P.R. Inc., Road 198 km 14.7 #100 Juncos Industrial Park, Juncos 00777-3873 Puerto Rico

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-951		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Isotretinoin	PROPRIETARY NAME (trade name) IF ANY CIP-ISOTRETINOIN CAPSULES	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) N/A	CODE NAME (If any) N/A	
DOSAGE FORM: Capsules	STRENGTHS: 10, 20, 30 and 40 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Severe recalcitrant nodular acne		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug <u>ACCUTANE® (isotretinoin) CAPSULES</u> Holder of Approved Application <u>Hoffmann-La Roche Inc.</u>			
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER			
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: <u>N/A</u>			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION Response to Information Request dated September 15, 2011 - Cetero Research			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED <u>1 (in triplicate)</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC			

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attachment providing Establishment Information.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DA # 21-951

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE

DATE:

Arthur M. Deboeck

Arthur M. Deboeck, VP & General Manager,
Galephar Pharmaceutical Research, Inc.

10/12/2011

ADDRESS (Street, City, State, and ZIP Code)

Telephone Number

US Agent, Galephar PR, Inc., Juncos, Puerto Rico, 00777-3873

(787) 713-0340

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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.

ESTABLISHMENT INFORMATION

DRUG SUBSTANCE

Manufacturing, Control & Testing:

(b) (4)



Site ready for inspection.

Last FDA inspection: (b) (4)

Outcome of last FDA inspection: Form FDA 483 issued.

All issues have been addressed to the satisfaction of FDA.

Contact Information for (b) (4)

(b) (4)



DRUG PRODUCT

Manufacturing & Bulk Drug Control & Testing:

Primary Blisters; Finished Packaged Product Stability & Release:

Galephar P.R. Inc.
Road 198 Km. 14.7 #100 Juncos Industrial Park,
Juncos, Puerto Rico 00777-3873
Tel: (787) 713-0340
Contact: Arthur Deboeck
CFN: 2650283

Site ready for inspection.

Last FDA inspection: (b) (4)

Outcome of last FDA inspection: No Form FDA 483 issued.

(b) (4)



Site ready for inspection.

Last FDA inspection: (b) (4)

No Form FDA 483 issued.



NDA 021951

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Cipher Pharmaceuticals Inc.
c/o Galephar P.R. Inc
ATTENTION: Arthur M. Deboeck
Vice President and General Manager, Galephar P.R. Inc.
Road 198 km 14.7 #100, Juncos Industrial Park
Juncos, Puerto Rico 00777-3873

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP isotretinoin Capsules 10, 20, 30 mg.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall

¹ These violations include studies conducted by [REDACTED] (b) (4) specific to the Houston, Texas facility.

development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Barbara Gould, Chief, Project Staff Management, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

BARBARA J GOULD

09/15/2011

p.p. DIVISION DIRECTOR Susan J. Walker



NDA 021951

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Cipher Pharmaceuticals Inc.
c/o U.S. Agent: Galephar P.R. Inc.
Road 198 km 14.7 #100
Juncos Industrial Park, Juncos, Puerto Rico 00777-3873

ATTENTION: Arthur M. Deboeck
Vice President and General Manager, Galephar P.R. Inc.

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) dated June 27, 2005, received July 1, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isotretinoin Capsules, 10 mg, 20 mg, 30 mg, and 40 mg.

We acknowledge receipt of your June 15, 2011 correspondence, on June 16, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4) from this NDA. This proposed proprietary name request is considered withdrawn from NDA 021951 as of June 16, 2011.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Matthew White at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
07/18/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-951

Cipher Pharmaceuticals Inc.
U.S. Agent: Galephar PR Inc
Attention: Jason A. Gross PharmD
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos, PR 00777-3873

Dear Dr. Gross:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP Isotretinoin Capsules 10, 20, 30mg.

We also refer to the meeting between representatives of your firm and the FDA on August 6, 2008. The purpose of the meeting was to discuss the proposed phase 3 clinical protocol submitted on July 4, 2008 under IND 64,927.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Elaine Smoot, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 6, 2008
TIME: 2:00 p.m – 3:30 p.m.
LOCATION: White Oak, Building 22, Conference Room 1313

APPLICATION: NDA 21-951: CIP-Isotretinoin Capsules
TYPE OF MEETING: Guidance
MEETING CHAIR: Susan J. Walker, MD

MEETING RECORDER: Elaine Smoot

FDA ATTENDEES:

Office of Drug Evaluation III

Maria R. Walsh, RN, MS, Project Management Officer

Division of Dermatology and Dental Products

Susan J. Walker, MD, Director

Jill Lindstrom, MD, Clinical Team Leader

Gordana Diglisic, MD, Medical Officer

Elaine Smoot, Regulatory Project Manager

Office of Drug Evaluation I

Division of Psychiatry Products

Victor Crentsil, MD, Medical Officer

Office of Clinical Pharmacology

Division of Clinical Pharmacology III

Edward D. Bashaw, PharmD, Director

Lydia Velazquez, PharmD, Team Leader

Office of Biostatistics

Division of Biometrics III

Kathleen Fritsch, PhD, Statistician

Office of Surveillance and Epidemiology

Division of Epidemiology

Andrew D. Mosholder, MD, Medical Officer

EXTERNAL CONSTITUENT ATTENDEES:

Cipher Pharmaceuticals, Ltd.

Larry Andrews, CEO and President

Jason A. Gross, PharmD, VP Scientific Affairs

Arshi Kizibash, MD, Medical Director

Julia Chan, RAC, Regulatory Affairs Manager

(b) (4)

Arthur Deboeck, Vice President, Galderma Pharmaceutical Research, Inc., U.S. Agent for Cipher Pharmaceuticals (via telephone)

BACKGROUND:

Cipher Pharmaceuticals Inc. submitted NDA 21-951, CIP-Isotretinoin Capsules for the treatment of severe recalcitrant acne vulgaris, on June 27, 2005. The April 25, 2007 approvable letter included the recommendation that the sponsor conduct a clinical trial in patients with severe recalcitrant nodular acne in which CIP-Isotretinoin is compared to Accutane at a dose of 1.0 mg/kg/day with adequate monitoring and evaluation of adverse events including psychiatric and CNS events, bone mineral density changes, hearing and vision impairment, and thorough follow-up of all patients with abnormal laboratory tests.

Meetings between Cipher and FDA were held on June 27, 2007 (Post-action discussion), July 11, 2007 (Formal Dispute Resolution), and October 1, 2007 (stalled development discussion). A guidance meeting was held on January 28, 2008 to discuss the design of a clinical study that will address FDA's concerns regarding the safety of CIP-Isotretinoin Capsules.

Cipher submitted a request on May 16, 2008 for a meeting to discuss a modified protocol design based on the comments received at the January 28, 2008 meeting. The meeting briefing package submitted on July 4, 2008 to IND 64,927 also included a request for a Special Protocol Assessment (SPA) for the modified protocol (ISOCT.08.01) entitled, "A Double-Blind, Randomized, Phase III, Parallel Group Study Comparing the Efficacy and Safety of CIP-ISOTRETINOIN to Accutane in Patients with Severe Recalcitrant Nodular Acne."

MEETING OBJECTIVES:

Purpose of the Meeting: To discuss the proposed phase 3 clinical protocol submitted on July 4, 2008 to IND 64,927.

Question 1:

The trial as proposed is based on a previous Accutane NF trial. The reason this trial was selected as the basis for study design is that it was the largest isotretinoin trial conducted to date, and was reviewed by the FDA. By minimizing differences between the study designs, the Accutane NF trial could potentially serve as a historical control for comparisons. With regard to the study the following questions are posed:

- a. The FDA suggested the use of an active control arm other than isotretinoin. In our response (Section 4) we have provided a rationale for not using an active control arm. Would it be acceptable not to include a third arm in this trial?

- b. The study population would consist of normal healthy individuals, diagnosed with severe recalcitrant acne. The FDA suggested that the inclusion criteria include Type I diabetes and to limit enrolment to just isotretinoin naïve subjects. In our submission, we have provided justification for including both isotretinoin naïve and non-naïve subjects, and are further proposing to exclude subjects with Type I diabetes. Is CIPHER's proposal acceptable to the Division?

Response:

- a. Yes. Your rationale for not using an active control arm other than isotretinoin is acceptable.
b. No.

As was previously recommended, the active treatment arms should include only subjects not previously treated with isotretinoin to avoid enriching the population with subjects who have successfully completed a prior course of treatment (e.g. eliminating patients who dropped out due to AE's). Additionally, this will allow for a better interpretation of safety data to be collected (see minutes of the January 28, 2008 meeting).

Your rationale for excluding subjects with controlled DM type I from the clinical trial is not clear. Please provide additional information regarding your proposal for excluding subjects with DM type I from the clinical trial. However, if you are concerned that such subjects may have a high rate of complications and that any imbalance in the randomization would confound the interpretation of results, you could stratify the randomization based on Type I diabetes status.

Discussion

CIPHER agreed with FDA's position about:

- Use of naïve/de novo subjects
- Subjects with Type I diabetes
- Excluding participants taking greater than the recommended daily allowance of Vitamin A (1000ug for males and 800ug for females)

Question 2:

The primary efficacy outcome measure is the change in total nodular lesion count (facial and truncal) at week 20 compared to baseline. The proportion of patients who achieve at least a 90% reduction from baseline to week 20 in the total number of nodular lesions (facial and truncal) will be used as a supportive analysis. Is this acceptable to the FDA?

Response:

1. FDA agrees with the endpoints and both endpoints are of interest to us. However, it is not clear what is meant by 'supportive analysis.' It is not clear whether the proposed endpoints are intended as co-primary endpoints or primary/secondary endpoints.
2. The primary efficacy endpoint should be the change in total nodular lesion (facial and truncal) at week 20 compared to baseline and the proportion of subjects who achieve at least a 90% reduction in the total number of nodules from baseline to week 20 (see minutes of the January 28, 2008 meeting).

3. The IGA scale should have a limited number of categories which are clinically meaningful, clearly defined, mutually exclusive, and non-comparative. The “Clear” category should represent true absence of disease.
4. Photographic examples of each grade that have been agreed with FDA before their use may be provided to investigators.

Discussion

- Cipher agreed that the proposed endpoints will be co-primary endpoints.

Question 3:

Regarding safety, the proposed trial will monitor emergent adverse events, and such events will be followed until adequate resolution. In addition to tracking emergent AEs, the FDA requested that specific body systems be measured; each has been addressed in the current submission in more detail:

- a. **Neuropsychiatric Events.** While there is no casual relationship established for neuropsychiatric events and isotretinoin treatment, the Division requested that such monitoring be conducted. Cipher has provided the monitoring plan in this submission. Is the methodology acceptable to the division? If not, what changes are suggested?

Response:

1. You have proposed a self-report instrument, the PHQ-9, as the only psychiatric assessment during treatment. Trials of the retinoid tazarotene included not only a self-report psychiatric instrument but a clinician assessment (the MINI), and direct questioning by clinical staff regarding mood and suicidal ideation.
2. Excluding patients with psychiatric disorders from the study might be protective of the subjects, but would limit the generalizability of the safety data on neuropsychiatric events.
3. Population PK data would be very helpful in interpreting any safety findings, especially if your formulation turns out to have greater bioavailability under study conditions than the marketed Accutane formulation.
4. Consideration should be given to setting up a Drug Safety Monitoring Board for this trial.
5. We agree with the exclusion of patients with an active mood disorder as well as those with a past history of suicidality. However, to enhance the generalizability of the results from the proposed study, we recommend that subjects with a personal history of a mood disorder, including depressive disorders, should not be excluded.
6. We have no objection to the use of the MINI-Plus modules for major depressive episode and suicidality in screening subjects. We suggest the inclusion also of other MINI-Plus modules, such as the screens for bipolar disorder and schizophrenia.

7. The PHQ-9 is considered a useful instrument for diagnosing and monitoring for changes in severity of depression in primary care settings. To improve the detection of other psychiatric symptomatology, we recommend the addition of the Brief Symptom Inventory (BSI-53) [See <http://www.pearsonassessments.com/tests/bsi.htm> for more information on the BSI-53]. We recommend prompt psychiatric referral if any subject meets one of the following criteria: a) a 25% or greater increase from baseline in the subscore for any of the nine psychopathology domains or b) an increase of at least two points or a subscore greater than or equal to three in the depression, hostility, or psychoticism domains. For PHQ-9, subjects who score ≥ 15 or a score of ≥ 1 on suicide-related question [Q.1(i)] at baseline or at any time during the trial monitoring should be discontinued from the study and promptly evaluated by a mental health professional.
8. We recommend the use of an adequate instrument to screen for and monitor the emergence of the spectrum of suicidal manifestations, such as the Columbia-Suicide Severity Rating Scale (C-SSRS). We recommend strongly use of the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to classify adverse events.
9. Since visits will occur monthly, subjects should be instructed to contact the investigator promptly if they develop substantial symptoms of depression, suicidality, mania, hostility, anxiety, psychosis, or cognitive decline between visits. We also recommend that during the conduct of the study, subjects who develop scores on any monitoring instrument suggestive of an active mood disorder should be discontinued from the study and promptly evaluated by a mental health professional.
10. For psychiatric ratings, different approaches to maximize the reliability and accuracy of psychiatric ratings in a dermatology practice population. As one approach, you may consider use an Interactive Voice Response System (IVRS) for patient self-report on symptoms of suicidal ideation or behavior. Another approach would be the use of a Centralized Expert Rating System to optimize subject screening and monitoring for psychiatric manifestations for all study sites. Both IVRS and centralized expert rating systems typically utilize remote methods. As a result, they should not replace the necessary vigilance of clinical investigators to avoid the emergence or worsening of adverse psychiatric manifestations such as suicidality.

Discussion

A discussion ensued about FDA's recommendation not to exclude subjects with a history of mood disorder; Cipher expressed concern about how to define a history of mood disorder (e.g., 3 or more episodes in lifetime; MMD episode prior to age 18; recently resolved episode < 5 yrs) so that subjects' exposure to risk is minimized and the data is not confounded given that the study is small. FDA noted that subjects will be closely monitored and advised Cipher that this safety study should be designed to reflect the actual patient population and evaluate the effect of isotretinoin on subjects with a history of mood disorder. FDA requested that Cipher provide additional details about the criteria for defining a history of mood disorder.

- Cipher agreed with the use of another module for the MINI-plus to detect bipolar disorder, but said that for schizophrenia, previous diagnosis by a health professional should suffice. FDA agreed. FDA recommended addition of a MINI-Plus module that screens for psychotic disorders.

- Cipher said FDA’s recommendation to include use of the BSI would add 9 additional assessment scales, many of which are not relevant to concerns raised with respect to isotretinoin. Other methodologies may be more appropriate. FDA said the PHQ-9 does not explore other psychiatric symptomatology that may be associated with isotretinoin. Cipher agreed to use the C-CASA to classify adverse events but believes that use of the C-SSRS should be used once a subject is referred to a mental health professional to categorize the suicidality. FDA said that PHQ-9 does not explore suicidality well enough to be used as a screening and monitoring tool. Following further discussion of the use of various neuropsychiatric evaluation tools, FDA recommended that Cipher propose monitoring methodologies and FDA will provide feedback.
 - The Agency asked for more detail as to who will conduct the initial neuropsychiatric disorders and the periodic evaluations.
- b. **Musculo-Skeletal.** A musculo-skeletal survey has been developed by Cipher in response to the Division's request. Is the proposed survey acceptable to the Division? If not, please clarify.
- c. **Audiology.** The current protocol has incorporated audiology testing at a subset of study sites as suggested by the Division. Is the audiology testing acceptable to the Division? If not, what changes are suggested?
- d. **Ocular.** Cipher has modified the protocol to use a best corrected visual acuity test will be standardized for the study, and will include a set of specific questions to elucidate emergent events, if such events occur. Is this acceptable to the Division? If not, what changes are suggested?
- e. **Bone Mineral Density.** Cipher has modified the protocol to exclude subjects with certain markers for bone metabolism disease as suggested by the Division. Further, the Division suggested that the study should incorporate measurements for premature epiphyseal closure and bone mineral density. Cipher has provided a detailed response to Division's comments on this issue, providing our rationale for not including this testing in the current trial. Is this acceptable? If not, what changes are suggested?

Response:

Responses to questions 4 (b), (c), (d), and (e) will be provided to you following our receipt of internal consultative reviews as indicated in our letter dated July 24, 2008.

Question 4:

The Division has suggested that population pharmacokinetics be included in the study design. Cipher has considered this recommendation, and provided comments within this submission (Section 4). Are the comments provided acceptable to the Division? If not, what changes are suggested?

Response:

At our January 28, 2008 meeting, you were advised to include in your study either a population pk component or geometric sampling of a limited number of subjects. We note that you have decided not to take our advice for reasons related to cost and complexity. We strongly disagree with this proposal as the pk data could be very informative (and possibly supportive) should there be an equivocal result from the clinical trial. While this portion of the phase 3 trial would not be necessary for approval (as the pk of your dosage form has been previously determined), the lack of such information to both refine the label and to inform the evaluation of the clinical portion of this study could have a negative outcome for you.

Discussions:

- Cipher said it has decided not to incorporate PK sampling into the study due to substantial issues associated with population pharmacokinetic studies most of which involve the accuracy of obtaining AUC, C_{max} , steady state and trough levels. Without proper controls, the results of a study can be difficult to interpret and/or will have confounding results.
- FDA recommended that samples be obtained at subjects' regular visits to provide information about "real world" usage. FDA said this type of usage information would be highly instructive for prescribers. In addition the FDA reiterated that this would be a population approach, not a "geometric sampling" approach, thus the number of blood samples required would be limited from each patient. As the objective would be to determine whether or not there was a significant separation in the steady-state levels between the subjects based on formulation, population modeling would be done on the data but not with the objective of demonstrating "bioequivalency".
- Cipher will respond to FDA's recommendations. This issue will be discussed further at another meeting.

Question 5:

Is the Statistical Analysis Plan proposed for the study acceptable to the Division? If not, what changes are suggested?

Response:

1. As safety issues are a key interest for this study, you should ensure that the study is adequately powered to detect safety events of interest. For the sample size calculations, the protocol should justify the magnitude of effect on neuropsychiatric, audiology, ocular and bone mineral density events that the study would be able to detect. In addition, the protocol should include details on how safety will be evaluated in the key areas where safety issues are of interest.
2. The proposed analysis for the change in total nodular lesions from baseline to week 20 appears to be similar to the analysis used in the Accutane NF trial. However, FDA would prefer that the analyses proposed for Protocol ISOCT.08.01 be selected because they are the most appropriate for the type of data, and not simply because they have been used in

previous studies. In particular, you should either provide justification for why the following features of the analysis are the most appropriate or provide an alternate proposal that may be more appropriate:

- square root transform of the nodule counts
 - use of the ratio of means rather than difference
 - choice of 0.866 as the boundary for the confidence intervals
3. The protocol should specify additional details about the proposed statistical methods. In particular, the methods for comparing proportions should be more completely described, specifying the particular methods that will be used. For example, will the confidence intervals be constructed using exact methods or normal approximations, will continuity corrections be used, etc.
 4. The protocol should provide additional details about the sensitivity analyses that will be performed to evaluate the impact of the primary method of imputing missing data.

Discussion

- In response to Cipher's question, FDA said it is possible that FDA may have additional comments about the proposed statistical plan in its response to the SPA. However, unless Cipher revises the protocol and addresses the issues raised here by FDA, it is unlikely that FDA will have any extensive additional comments.
- Cipher asked if methodologies using the last observation carried forward (LOCF) for handling missing data is acceptable. FDA responded that LOCF may be acceptable for the primary method and recommended that Cipher propose several sensitivity analyses.

Question 6:

If the study is conducted as mutually agreed between FDA and Cipher, and is deemed to be a positive study, Cipher understands that there are no other clinical issues that will be required as a condition of approval. Is Cipher's understanding correct? If not, please clarify.

Response:

After agreement on the conduct and design of the clinical trial is reached between you and FDA, the approval for your product will be a review issue.

Question 7:

Cipher understands that the labeling for the product will indicate that CIP-ISOTRETINOIN may be administered without regard to meals, based on the pharmacokinetic data, and the lower variability between fed and fasted states, and if the clinical study is positive and deemed adequate to support product approval. Is this correct? If not, please clarify.

Response:

Labeling for the product is a review issue.

ACTION ITEMS:

1. Cipher will provide responses to FDA's recommendations regarding the monitoring plan for neuropsychiatric events, the statistical analysis plan, and population pharmacokinetics,
2. Per FDA's letter of July 24, 2008, FDA will respond to Cipher's July 4, 2008 request for SPA following receipt of the consultative reviews of multiple internal consultants.
3. Another meeting will be held with Cipher following FDA's response to the SPA request.

ATTACHMENTS/HANDOUTS: Cipher's slides presented at today's meeting to guide the discussion are attached.

CIPHER PHARMACEUTICALS

August 6, 2008

Agenda

2

- Introduction
- Attendees
- Discussion of Cipher's SPA questions
- Comments or recommendations from the Agency
- Concluding remarks

FDA Attendees

3

- Susan Walker, MD - Director: Division of Dermatology and Dental Products
- Jill Lindstrom, MD - Clinical Team Leader: DDDP
- Gordana Diglisic, MD - Medical Officer: DDDP
- Kathleen Fritsch - Statistician: Division of Biometrics
- Edward D. Bashaw, Pharm.D. - Director: Division of Clinical Pharm III
- Andrew Mosholder, MD - Medical Officer: OSE, Division of Epidemiology
- Rita Quellet-Hellstrom - Epidemiologist: OSE, Division of Epidemiology
- Maria Walsh - Project Management Officer: ODE III
- Elaine Smoot - Regulatory Project Manager: DDDP

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Cipher Attendees

4

- Larry Andrews - President & CEO, Cipher Pharmaceuticals Inc.
- Jason A. Gross, Pharm.D. - VP, Scientific Affairs, Cipher Pharmaceuticals Inc.
- Arshi Kizilbash, MD - Medical Director, Cipher Pharmaceuticals Inc.
- Julia Chan, RAC - Regulatory Affairs Manager, Cipher Pharmaceuticals Inc.

(b) (4)

BY TELECONFERENCE

(b) (4)

- Arthur Deboeck - VP & General Manager, Galephar Pharmaceutical Research Inc, US Agent for Cipher

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FDA Discussion Points

5

- Study Logistics
 - Primary Efficacy Endpoint
 - Statistical Analysis Plan
 - Study Duration Should be 20 Weeks
 - 4-Week Follow-Up
 - Reference Listed Drug - Approved Generic
- Study Enrollment
 - Non-Isotretinoin Study Arm
 - Exclusion of Subjects with a Psychiatric History
 - Use of Naïve/de novo Subjects
 - Subjects with Type I Diabetes
 - Vitamin A, which is 1000 µg - Exclusion
- Study Assessments
 - Neuropsychiatric Events
 - Laboratory Assessments
 - Musculoskeletal Survey
 - Bone Mineral Density
 - Visual Screening Exam
 - Audiology Testing (subset of subjects)
 - Population Kinetics
- Administrative
 - Product Labeling (Dosing with Food)

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Study Logistics

Primary Efficacy Endpoint

6

FDA Comment

FDA agrees with the endpoints and both endpoints are of interest to us. However, it is not clear what is meant by 'supportive analysis.' It is not clear whether the proposed endpoints are intended as co-primary endpoints or primary/secondary endpoints.

Cipher

The primary efficacy endpoint should be the change in total nodular lesion (facial and truncal) at week 20 compared to baseline and the secondary proportion of subjects who achieve at least a 90% reduction in the total number of nodules from baseline to week 20

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Statistical Plan

7

FDA Comment

Question 5, #1-4

- 1. As safety issues are a key interest for this study, you should ensure that the study is adequately powered to detect safety events of interest...
- 2. The proposed analysis for the change in total nodular lesions from baseline to week 20 appears to be similar to the analysis used in the Accutane NF trial. ...
- 3. The protocol should specify additional details about the proposed statistical methods...
- 4. The protocol should provide additional details about the sensitivity analyses ...

Cipher

The FDA response requires some additional internal discussions.

Question:

- Will additional comments be provided with the SPA review?
- For missing data is methodologies using LOCF acceptable?

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Study Enrollment

Exclusion of Subjects with a Psychiatric History

8

FDA Comment

Question 3.a.5.

We agree with the exclusion of patients with an active mood disorder as well as those with a past history of suicidality. However, to enhance the generalizability of the results from the proposed study, we recommend that subjects with a personal history of a mood disorder, including depressive disorders, should not be excluded.

Cipher

We agree to exclude pts. with an active mood disorders as well as a past history of suicidality.

Can FDA clarify comment:

- High relapse rate Vs. general population.
- History of 3 or more episodes in lifetime.
- MMD episode prior to age 18
- Recently resolved episode < 5 yrs (guidelines risk of relapse)

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Neuropsychiatric Events

9

FDA Comment

Question 3.a.6

We have no objection to the use of the MINI-Plus modules for major depressive episode and suicidality in screening subjects. We suggest the inclusion also of other MINI-Plus modules, such as the screens for bipolar disorder and schizophrenia.

Cipher

Agree that the use of another module for the Mini-plus to detect Bipolar Disorder, however, for Schizophrenia, previous diagnosis by a health professional should suffice.

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Neuropsychiatric Events

10

FDA Comment (Question 3.a.7)

The PHQ-9 is considered a useful instrument for diagnosing and monitoring for changes in severity of depression in primary care settings. To improve the detection of other psychiatric symptomatology, we recommend the addition of the Brief Symptom Inventory (BSI-53). . .

Cipher

- The PHQ-9 is highly sensitive for detecting mood changes, and suicidality.
- Literature reviews has reveled that multiple assessment methodologies do not improve sensitivity.
- Question : The BSI is adding not 1 but 9 additional assessment scales many of which are not relevant to concerns raised with respect to isotretinoin. Other methodologies may be more appropriate.

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Neuropsychiatric Events

11

FDA Comment

Question 3.a.8

We recommend the use of an adequate instrument to screen for and monitor the emergence of the spectrum of suicidal manifestations, such as the Columbia-Suicide Severity Rating Scale (C-SSRS).

We recommend strongly use of the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to classify adverse events.

Cipher

Cipher has considered the C-SSRS, it is a clinician administered assessment methodology with a series of questions that ask various questions about suicidal ideations and behaviors.

Once a subject is referred to a mental health professional for a positive response, we believe that the C-SSRS would be the assessment tool for categorizing the suicidality.

Cipher agrees: The C-CASA will be used to classify adverse events.

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Population Kinetics

12

FDA Comment

One of the on-going points of disagreement with the Agency and Cipher has been the question of whether with real world use there would be a separation of blood levels of isotretinoin due to the differential food effect. While the current study design, once agreed upon with FDA input, will be able to address the global safety issue, it will not address this issue of differential bioavailability. We strongly encourage the sponsor to incorporate into the trial pharmacokinetic sampling along the lines of either of the following two options:

1. A population pharmacokinetic sampling scheme where a limited number of samples will be collected over the entire study interval in all subjects.
2. A classical geometric pharmacokinetic sampling program in a limited number of individuals in all treatment arms. The sampling profile should include day one, mid-point, and final dose pk profile sampling along with trough samples at selected time points during treatment at study visits.

Cipher

With regard to the population PK study, during the last FDA meeting Dr. D. Bashaw specified that this is not a requirement and only an option, and while FDA would encourage Cipher to conduct a population PK study it is not a requirement.

Due to substantial issues associated with population pharmacokinetic studies; most of which involve the accuracy of obtaining AUC, C_{max}, steady state and trough levels. Without proper controls the results of a study can be difficult to interpret and/or will have confounding results. Therefore Cipher has considered the FDA's recommendation. However, we have decided not to incorporate PK sampling into the study.

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Product Labeling (Food)

13

FDA Comment

Dr. Beitz indicated in her letter of October 25, 2007, that if a clinical study was acceptable the Agency would be prepared to permit labeling which would indicate the product could be taken without regard to meals.

The Division concurs, provided adequate data is provided from the clinical study.

Cipher

Cipher acknowledges the comment, and understands this to mean - if the study as proposed is deemed adequate to support the approval of the NDA, the product could be labeled to be taken without regard to meals. A proposed package insert including this anticipated claim has been provided.

August 5, 08, Comment:

Labeling for the product is a review issue

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/s/

Susan Walker

9/5/2008 04:08:55 PM

From: Tisha Washington
Sent: June 4, 2008
To: Jason A. Gross, Pharm.D.
Subject: NDA 21-951: Type B Meeting Confirmation

Dr. Gross,

This fax serves to confirm the scheduling of a Guidance meeting for CIP-Isotretinoin Capsules for the treatment of severe recalcitrant nodular acne. Please let me know as soon as possible if this date and time are acceptable to you.

DATE: August 6, 2008

TIME: 2:00 pm EST

LOCATION: FDA Research Center at White Oak
10903 New Hampshire Avenue, Building 22
Silver Spring, MD 20993

FDA PARTICIPANTS:

Susan Walker, M.D./Division Director, DDDP
Stanka Kukich, M.D./Deputy Director, DDDP
Jill Lindstrom, M.D./Clinical Team Leader, DDDP
Gordana Diglisic, M.D./Clinical Reviewer, DDDP
Bronwyn Collier/Associate Director for Regulatory Affairs, ODEIII

Please submit the background information for this meeting at least two weeks prior to the meeting date. Three archival copies should be sent to the Ammendale Road address and 15 *bound* copies each marked "DESK COPY", to the attention of Tisha Washington at the above address, **Room 5164**. If we do not receive it by July 7, 2008, we may need to cancel the meeting.

Thanks,
Tisha Washington
Technical Information Specialist
Division of Dermatology and Dental Products
P: (301) 796-2110
F: (301) 796-9895

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this page is the manifestation of the electronic signature.**

/s/

Tisha Washington
6/4/2008 05:16:56 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.
Attention: Arthur Deboeck, Vice President and General Manager
Road 198 km 14.7 #100 Juncos Industrial Park
Juncos 00777-3873 Puerto Rico

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10 mg, 20 mg, and 30 mg.

We also refer to the meeting between representatives of your firm and the FDA on January 28, 2008. The purpose of the meeting was to discuss the design of a potential clinical study in order to address the Agency's concerns regarding the safety of CIP-Isotretinoin Capsules.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: January 28, 2008 **Time:** 1:00 P.M.
Location: WO1415 **Meeting ID:** 23393
Topic: NDA 21-951, CIP-Isotretinoin Capsules 10 mg, 20 mg, and 30 mg
Subject: Guidance meeting
Regulatory Path: 505(b)(2)
RLD: Accutane (isotretinoin) Capsules
Sponsor: Cipher Pharmaceuticals, Ltd.
Meeting Chair: Susan Walker, M.D./Division Director, DDDP
Meeting Recorder: Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

FDA Attendees:

Susan Walker, M.D./Division Director, DDDP
Stanka Kukich, M.D./Deputy Division Director, DDDP
Julie Beitz, M.D./ Director, ODE III
Markham C. Luke, M.D., Ph.D./Lead Medical Officer, Dermatology, DDDP
Denise Cook, M.D./Clinical Reviewer, DDDP
Jill Lindstrom, M.D./Lead Medical Officer, Dermatology, DDDP
Gordana Diglisic, M.D./Clinical Reviewer, DDDP
Andrew Mossholder, M.D./Medical Officer, OSE
Dennis Bashaw, Pharm.D./Director, DCPIII, HFD-880
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP, HFD-540

Sponsor Attendees:

Cipher Pharmaceuticals, Ltd.

Larry Andrews/President, CEO
Julia Chan/Regulatory Affairs Manager
Arshi Kizilbash, M.D./Medical Director

Arthur Deboeck/Vice President and General Manager, Galephar PR, Inc., U.S. Agent

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Purpose:

To provide general guidance on the content and format of the New Drug Application under 21CFR 314. The pre-meeting briefing document (submitted January 11, 2008) provides background and questions (p 3) for discussion. The sponsor requests input from the Agency on the design of a potential clinical study in order to address the Agency's concerns regarding the safety of CIP-Isotretinoin.

The Division acknowledges the sponsor's concerns about conducting a clinical trial. Our concern about the differential bioavailability of Cipher vs. innovator isotretinoin provides the basis for our concern that there may be an impact on the safety profile. We are prepared to work with you, including additional meetings and rapid protocol reviews, in order to arrive at an agreement on the study design and final protocol elements.

Clinical

Question 1:

The basic design of the proposed trial (Appendix 1) will be based on that of the Accutane NF trial (Appendix 2), with the major exception being the way in which the test and reference products are dosed. Both products would be dosed at the same mg/kg/d dose and administered with food as specified in the currently approved labeling. Dosing both the test and reference products with food (the contents of which would be unspecified), will maximize the upper range of exposure for CIP-ISOTRETINOIN, and hence address the safety concern raised by the Division. Is this study design acceptable to the Division?

Response:

The protocol should include adequate assessment of neuropsychiatric events, including depression, impulsive behavior, and suicidal ideation. There was discussion concerning the inadequacy of the Beck depression score as the sole an evaluation instrument, and the sponsor is encouraged to develop an evaluation schedule and timetable that best evaluate the potential NS safety concerns. The timing of evaluations should be carefully considered and justified. Consideration should be given to adding mental health clinicians as clinical investigators for the purpose of performing the neuropsychiatric assessments. Exclusion of subjects with a psychiatric history would be protective if such patients are indeed more vulnerable to neuropsychiatric adverse events, but would preclude collection of safety data in that potentially vulnerable group. The sponsor is encouraged to interact with the division during the development of the neuropsychiatric assessment plan.

With the next protocol submission, the sponsor should also address the study arms, including consideration of whether including a comparator arm of patients who are not taking isotretinoin would allow better interpretation of any potential neuropsychiatric events.

The active treatment arms should include only individuals NOT previously treated with isotretinoin to avoid enriching the population with patients who have successfully completed a prior course of treatment. (i.e. eliminating patients who dropped out due to AE's).

Question 2:

Would the data from the proposed study permit the Division to approve the product, if the study is successful?

Response:

Approval of an NDA is based upon review of the entire 505(b)(2) package. It would certainly be anticipated that following agreement with the Agency on study design, a successful trial would support approval

Question 3:

Are there any changes or additional criteria the Division requires in the study design?

Response:

- The usual course of treatment with Accutane is 20 weeks. This should be the primary endpoint for efficacy analysis. If subjects clear prior to 20 weeks after at least 15 weeks of treatment, then such subjects would be considered a success provided efficacy was maintained at week 20.
- Patients recruited into the study should be “de novo” subjects who have not been exposed to isotretinoin in the past or any other oral retinoid. This will allow for a better interpretation of safety data to be collected.
- The primary efficacy endpoint should be the change in total nodular lesion (facial and truncal) count at week 20 compared to baseline (LOCF) and the proportion of subjects who achieve at least a 90% reduction in the total number of nodules from baseline to week 20.
- It is noted in the study schedule that laboratory assessments will be made at screening, baseline, and weeks 4, 8, 12, 16, and 20 to include hematology, serum chemistry, urinalysis, and lipid profile. A lipid profile and LFTs should also be done at week 2. This will add in determining a response to the oral retinoid or lack thereof. Serum chemistry should include LFTs, serum calcium, phosphates, and CPK.
- There should be a 4 week follow-up at week 24 with assessments made as necessary.
- The sponsor should develop a musculoskeletal survey to be administered at each follow-up visit evaluating all musculoskeletal events, including pain during treatment.
- It is recommended that subjects with controlled type 1 diabetes be allowed into the trial
- Subjects should not be allowed to have greater than the recommended daily allowance of Vitamin A, which is 1,000 ug for males and 800 ug for females.
- A subset of subjects should have full audiology testing looking for changes in high frequency
- Visual screening exams should use best corrected visual acuity and for any development of night blindness, an electroretinogram should be performed.

For pediatric subjects, ages 12-17 years, the effects of Cip-isotretinoin on bone metabolism in a growing adolescent after a 20-week course needs to be evaluated. To this end the sponsor should incorporate the following into the protocol:

- Baseline serum 25-hydroxyvitamin D levels

- Baseline and final visit DEXA (dual x-ray absorptiometry) scan of the non dominant hip and A/P lumbar spine to measure bone mineral density
- Lateral plain film of the cervical spine
- The sponsor should determine a method evaluating whether early closure of the epiphysis occurs. Assessments may include Tanner staging for pubertal maturity, age of menarche for females, x-rays, etc.
- Subjects with adverse changes in BMD need to be followed for an additional 6 months after the last dose of study drug.
- Pediatric subjects with HLA-B27 related disease, rheumatoid arthritis, rickets or other Vitamin D depletion disease or phosphate metabolic disease, severe scoliosis > 15 Cobb angle, history of back surgery/injuries, or presence of cervical hyperostosis at baseline should be excluded.

Question 4:

Could the final protocol be evaluated and approved under the “Special Protocol Assessment” program, as suggested by Dr. Beitz in her letter dated October 25, 2007 (Appendix 3)?

Response:

Yes, after sufficient discussion has taken place with the Agency.

Question 5:

Would it be acceptable to the Division for Cipher to use an approved generic as the comparator in the study instead of Accutane, as this would mean savings of at least \$1 million, due to the cost difference between the brand and generic products?

Response:

The current guidance provided by the Agency requires that the sponsor use a "listed drug", ie. a drug product listed in the FDA "Orange Book". Comparators for 505(b)(2) products need not be "reference drug products" as a drug listed in the "Orange Book" as an AB rated product is assumed to be bioequivalent and thus interchangeable with the innovator product. Thus the use of an AB rated generic version of Accutane is allowable. The sponsor may, however, find it more advantageous to use the innovator product so as to more tightly bind their findings to the innovator product and any published data they may wish to further reference in support of their submission.

Question 6:

Dr. Beitz indicated in her letter of October 25, 2007, that if a clinical study was acceptable the Agency would be prepared to permit labeling which would indicate the product could be taken without regard to meals. Does the Division concur?

Response:

Yes, provided adequate data is provided from the clinical study.

Additional Comments:

One of the on-going points of disagreement with the Agency and Cipher has been the question of whether with real world use there would be a separation of blood levels of isotretinoin due to the differential food effect. While the current study design, once agreed upon with FDA input, will be able to address the global safety issue, it will not address this issue of differential bioavailability. We strongly encourage the sponsor to incorporate into the trial pharmacokinetic sampling along the lines of either of the following two options:

1. A population pharmacokinetic sampling scheme where a limited number of samples will be collected over the entire study interval in all subjects.
2. A classical geometric pharmacokinetic sampling program in a limited number of individuals in all treatment arms. The sampling profile should include day one, mid-point, and final dose pk profile sampling along with trough samples at selected timepoints during treatment at study visits.

As has been indicated previously in the clinical discussion, in order to properly characterize the profiles over time, subjects should received no more and certainly no less instruction on the administration of isotretinoin with food than the clinician would normally give during a standard course of isotretinoin therapy in their current practice. On days where PK sampling will occur, the subject, upon arrival at the study unit will be asked to fill out a dietary history for the preceding meal and any intervening snacks along with the time. Subjects should not be told of the need to fill this form out prior to arrival at the study unit to preclude any alteration to their normal dietary habits (so as to deter a biasing of the meal content).

Administrative Comments

1. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain and assessment of the safety and effectiveness of the pediatric patients unless this requirement is waived or deferred.
2. 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. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

Minutes Preparer: _____
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

Chair Concurrence: _____
Susan J. Walker, M.D./Division Director, DDDP

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/s/

Susan Walker
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NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Inc.
Attention: Jason Gross, PharmD, VP, Scientific Affairs
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Dr. Gross:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10 mg, 20 mg, and 30 mg.

On May 29, 2007, you requested a formal dispute resolution concerning the Division of Dermatology and Dental Products' (DDDP's) decision to issue an approvable letter for NDA 21-951, CIP-Isotretinoin Capsules, on April 25, 2007. DDDP determined that the NDA did not establish an adequate basis for the Agency to rely for approval of CIP-Isotretinoin Capsules upon its previous finding of safety for Accutane. Review of your appeal was deferred until after a post-action meeting was held with your firm and DDDP on June 27, 2007. On June 28, 2007, you resubmitted your original formal dispute resolution request, and a meeting was held at your request on July 11, 2007 with Drs. Robert Temple and Susan Walker, Ms. Elizabeth Dickinson from FDA's Office of Chief Counsel, and me. In a letter dated August 10, 2007, I upheld DDDP's approvable action.

On September 17, 2007, you requested a meeting with Drs. Temple and Walker, Ms. Dickinson and me to discuss the concerns raised in the August 10, 2007 letter before proceeding with the appeal process. This meeting was held on October 1, 2007. In a follow-up letter dated October 9, 2007, you requested that I reconsider my appeal decision of August 10, 2007 and determine that CIP-Isotretinoin's safety is established by FDA's previous determinations for Accutane.

My comments will focus on several issues that you raised at the October 1, 2007 meeting and subsequently in your October 9, 2007 letter.

A. Hoffman La Roche's 600-patient randomized controlled trial of Accutane vs. Accutane NF "revalidates the safety and efficacy of Accutane when taken with food."

While the Agency's review identified no new efficacy or safety concerns for Accutane in this study, I concur with your quoted statement by the reviewing medical officer that "inconsistency in implementation [of protocol procedure] significantly affects interpretation of the safety results

in this comparison trial.” With regard to the occurrence of psychiatric adverse events and discontinuations due to psychiatric symptoms, the medical officer concluded in 2000 that the study design and conduct precluded reliable case assessment in retrospect, and the variability in the recording of events and patient follow-up raised concerns about reporting bias.¹ I concur with the medical officer’s conclusions and would add that these concerns apply to both treatment groups.

Moreover, in the years since this study was completed, increasing numbers of spontaneous post-marketing reports of psychiatric adverse events in association with Accutane use have become a serious concern for the Agency. Although the Agency’s position has been, and continues to be, that a causal relationship has not been established for isotretinoin with respect to psychiatric adverse events, in recent years it has taken steps to maximize patient safety by recommending stronger warnings in product labeling regarding pre-treatment evaluation and continued patient monitoring for potential psychiatric risks before and during isotretinoin therapy.

B. The results of Hoffman La Roche’s controlled trial comparing Accutane to Accutane NF do not “prevent CIP-Isotretinoin’s reliance on FDA’s safety determination for Accutane.”

This statement highlights the fundamental difference in our views. I believe you can rely on the Agency’s efficacy determination for Accutane as evidenced by this study and other Accutane trials. However, I am not prepared to assume that the different pharmacokinetic profile of CIP-Isotretinoin relative to Accutane has no impact on the safety profile of your product. Specifically, CIP-Isotretinoin has not been demonstrated to be bioequivalent to Accutane under both fed and fasted conditions. Exposures to your product can be expected to lie in the upper range of exposures for Accutane due to the lower absorption of Accutane under fasted conditions. Given that Accutane is not consistently taken with food in real world use², it is reasonable to assume that Accutane users experience a wide range of exposures all of which contribute (both high and low exposures) to the overall safety profile of Accutane. As has been previously stated, a controlled trial which randomizes patients to receive either Accutane or CIP-Isotretinoin and which incorporates pharmacokinetic sampling would address potential differences in isotretinoin exposure and in the safety profile of these two formulations in patients receiving a typical course of therapy.

C. “Accutane NF may not be bracketed by Accutane.”

You have made several technical points regarding the pharmacokinetic profile of Hoffman La Roche’s Accutane NF relative to Accutane. I have reviewed publicly available documents related to the Accutane NF NDA as well as reviews from the medical and clinical pharmacology staff. After conferring further with Dr. Walker and Dr. Dennis Bashaw (from CDER’s Office of Clinical Pharmacology) I continue to uphold our previously held position that Accutane NF exposures may be bracketed by Accutane exposures. Our collective interpretation of the major findings regarding Accutane NF exposures relative to Accutane exposures can be summarized as follows:

¹ See transcript from the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting held September 19, 2000, page pp. 276-277

² *Ibid.*, page 243, description of Hoffman La Roche’s survey of prescribing practices

- In a study comparing single dose pharmacokinetics of Accutane NF relative to Accutane, plasma concentration-time curves showed that Accutane exposures under fed and fasted conditions bracketed fed and fasted Accutane NF exposures for the doses tested. In this study, the difference in exposure for Accutane administered under fed conditions relative to fasted conditions was 240%, whereas the difference in exposure for Accutane NF under fed conditions relative to fasted conditions was only 30%. *Relative to the food effect seen with Accutane*, the Agency concluded that the food effect seen with Accutane NF was an “insignificant change”.³
- Using the exposure data from the single dose pharmacokinetic study, but with *doses normalized*, an Accutane NF dose of 0.4 mg/kg under fed or fasted conditions was roughly equivalent to an Accutane dose of 0.5 mg/kg under fed conditions. In the controlled trial, Hoffman La Roche compared Accutane NF 0.4 mg/kg *once daily* with Accutane 0.5 mg/kg *bid*. The two treatment regimens were similarly effective.
- No pharmacokinetic sampling was performed in the controlled trial. The Agency performed *simulations* of steady-state exposures using simple computational methods to predict isotretinoin exposures in patients over the course of their treatment. We believe these simulations are an idealized depiction of steady-state exposures that do not take into account fat content of meals and host factors, such as, but not limited to, diurnal changes in ACTH-cortisol regulation and other inter- and intra-patient sources of variability. In the absence of actual steady-state data from patients, we do not consider these simulations to be accurate reflections of steady-state exposures in patients receiving a 20-week course of isotretinoin treatment, especially in light of the differences in dosing as described in the bullet above. Specifically, we cannot conclude that the steady-state exposures for either Accutane NF fed, Accutane NF fasted, or Accutane fasted, as predicted for the 12 - 24 hour period, are appreciably different.⁴ Thus, we believe that Accutane NF exposures may be bracketed by Accutane exposures.
- Your sketch of steady-state exposures in patients treated with Accutane NF or Accutane in the controlled trial overly exaggerates the differences between the two treatment groups.

D. “Is the observation in the Accutane NF clinical trial real?”

You have questioned whether the imbalance in psychiatric adverse events identified in Accutane NF-treated patients in the Hoffman La Roche controlled trial was real and provided reasons why the signal could not be a function of higher plasma isotretinoin levels if it were real. As you know, this issue was raised before a panel of experts at the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting held September 19, 2000. Although no obvious explanation could be put forward to account for the apparent imbalance, the Agency was unwilling to dismiss the observation as a chance finding.

In summary, unlike approved generic isotretinoin products, CIP-Isotretinoin is bioequivalent to Accutane under fed conditions but not bioequivalent under fasted conditions. Given the less

³ *Ibid.*, page 267, presentation by Dr. Dennis Bashaw

⁴ CIPHER presentation, October 1, 2007

variable absorption of your product when taken under fed and fasted conditions, and the increased bioavailability of your product relative to Accutane under fasted conditions, CIP-Isotretinoin could represent an advance in the treatment of severe recalcitrant nodular acne. However, if approved, there should be no need to label CIP-Isotretinoin with a food limitation. Lastly, while I acknowledge the limitations in our understanding of the pharmacokinetic and safety profiles of Accutane NF, I am not prepared to dismiss the Agency's prior experience with the product.

Given that your product does not meet the bioequivalence standards for approval in an abbreviated new drug application, I cannot assume that CIP-Isotretinoin will be comparable to Accutane in terms of safety. Therefore, I conclude that clinical studies would be needed to adequately characterize the safety profile of CIP-Isotretinoin prior to approval.

As stated in my August 10, 2007 letter, I would encourage you to work closely with the Division of Dermatology and Dental Products to develop a suitable prospective safety study of CIP-Isotretinoin. Request for review of the study protocol under a special protocol assessment is strongly recommended.

Alternatively, you could consider reformulating your product so that it meets bioequivalence standards for approval in an abbreviated new drug application as a generic product.⁵

If you wish to appeal this decision to the next level, your request will be directed to Dr. John Jenkins, Director of the Office of New Drugs. If you have any further questions, please contact Ms. Grace Carmouze, Formal Dispute Resolution Project Manager, at 301-796-1654.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

⁵ Suggestion previously communicated to you in a 74-day letter from DDDP dated October 26, 2005

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/s/

Julie Beitz
10/25/2007 11:02:58 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Inc.
Attention: Jason Gross, PharmD., VP, Scientific Affairs
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Dr. Gross:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10 mg, 20 mg, and 30 mg.

We also refer to the meeting between representatives of your firm and the FDA on October 1, 2007. The purpose of the meeting was to discuss the issues raised in my August 10, 2007 response to your June 28, 2007 formal dispute resolution appeal.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Maria R. Walsh, Project Management Officer, at (301) 796-1017.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 1, 2007
Time: 12:00 p.m. – 1:00 p.m.
Location: White Oak, Building 22, Conference Room 1313

Application: NDA 21-951: CIP-Isotretinoin Capsules
Type of Meeting: Stalled Development Discussion

Meeting Chair: Julie Beitz, MD
Meeting Recorder: Maria R. Walsh, RN, MS

FDA Attendees:

Office of Drug Evaluation III
Julie Beitz, MD, Director
Maria R. Walsh, RN, MS, Project Management Officer
Division of Dermatology and Dental Products
Susan Walker MD, Director

Office of Medical Policy
Robert Temple, MD, Director

Office of Chief Counsel
Elizabeth Dickinson, Esq.

External Constituents Attendees:

Cipher Pharmaceuticals, Ltd.
Larry Andrews, CEO and President
Jason A. Gross, Pharm.D, VP Scientific Affairs

(b) (4)

Background: Following a July 11, 2007 meeting between representatives of Cipher Pharmaceuticals and FDA, Dr. Julie Beitz responded to Cipher Pharmaceuticals' June 28, 2007 formal dispute resolution request on August 10, 2007 and upheld the approvable action taken on April 25, 2007 by the Division of Dermatology and Dental Products on NDA 21-951, CIP-Isotretinoin Capsules, 10mg, 20 mg, and 30 mg for the treatment of severe recalcitrant nodular acne.

The April 25, 2007 approvable letter states, in part, that “the application did not establish an adequate basis for the Agency to rely on our previous finding of safety for the listed drug, Accutane,” because it did not demonstrate “that the difference in the pharmacokinetic profile of CIP-Isotretinoin as compared to Accutane is not clinically meaningful with regard to the safety profile of CIP-Isotretinoin.” The approvable letter includes the Division’s recommendation that

the sponsor conduct a clinical trial in patients with severe recalcitrant nodular acne in which CIP-Isotretinoin is compared to Accutane at a dose of 1.0 mg/kg/day.

Dr. Beitz's August 10, 2007 letter states, in part, that our experience with Hoffman LaRoche's proposed Accutane NF formulation "suggests that a difference in bioavailability of isotretinoin products could be important" with regard to safety. "Compared with Accutane-treated patients, more patients treated with Accutane NF reported psychiatric events (11 vs. 1) and more patients discontinued the study for psychiatric symptoms (4 vs. 0). Dr. Beitz concluded that "the bioequivalence studies performed to date with CIP-Isotretinoin evaluated too few patients for very short durations and were not properly designed to assess its overall safety profile relative to Accutane under conditions of use."

On September 17, 2007, the sponsor requested a meeting with Dr. Beitz, Dr. Robert Temple, Dr. Susan Walker, and Ms. Elizabeth Dickinson to discuss the concerns raised in the August 10, 2007 letter before proceeding with the appeal process.

Meeting Summary:

Presentation

The sponsor began the meeting with a presentation (see attached slides). During the presentation, the sponsor made the following main points:

- Plasma levels of Accutane and CIP-Isotretinoin are the same under fed conditions. Under fasted conditions, plasma levels of CIP-Isotretinoin fall in-between the levels of Accutane fed and fasted.
- The conditions of use for Accutane NF (0.4 mg/kg/d, taken QD without regard to food) are not the same as the proposed conditions of use for CIP-Isotretinoin (0.5-2.0 mg/kg/d, taken BID with food). Rather, the proposed conditions of use of CIP-Isotretinoin are the same as those for Accutane.
- Accutane taken under fed conditions has been determined by FDA to be safe and effective. This finding was revalidated by the Hoffman La Roche study comparing Accutane NF to Accutane in that the occurrence of neuropsychiatric events were lower in the Accutane arm (under fed conditions representing the maximum plasma levels) vs. the Accutane NF arm.
- "Real world" exposure with CIP-Isotretinoin would be no more than the "ideal world" exposure (study conditions - fed) with Accutane which was deemed safe in the Hoffman La Roche comparative study.
- A causal link between neuropsychiatric events and isotretinoin has not been established and there is no evidence of a dose-response relationship. Moreover, Accutane NF, with a dose of 0.4 mg/kg/day, produced blood levels far lower than the Accutane control group,

given at 1 mg/kg/day in a BID dose. It is therefore highly implausible to think that the neuropsychiatric events were related to better absorption and higher blood levels.

- CIP-Isotretinoin should be able to rely on FDA's previous finding of safety and efficacy for Accutane under the conditions prescribed, recommended, or suggested in the proposed labeling.

Discussion

- FDA said that under "real world" conditions, where patients may or may not take isotretinoin with food, patients taking CIP-Isotretinoin may be exposed to a higher level of isotretinoin than patients taking Accutane because the relative bioavailability of CIP-Isotretinoin fasted is approximately twice that of Accutane fasted (65% vs. 33%).
- FDA said that although a causal link between neuropsychiatric events and isotretinoin has not been established, these events have been a safety concern since the approval of Accutane. Because the pharmacokinetic profiles of Accutane and CIP-Isotretinoin are different, the safety profile of CIP-Isotretinoin may also be different as observed by the results of the Hoffman La Roche study comparing Accutane NF to Accutane. Therefore, a clinical trial comparing CIP-Isotretinoin to Accutane is needed to establish the safety of CIP-Isotretinoin.
- The sponsor reiterated that the Hoffman La Roche comparative study, the largest study with Accutane to date, in which Accutane was taken under fed conditions for five months, re-establishes Accutane's safety under the conditions recommended in the approved labeling (i.e. taken with food). CIP-Isotretinoin should be able to rely on this finding of safety because the bioavailability of CIP-Isotretinoin fed is equivalent to that of Accutane fed and when taken fasted, it is within the upper range of Accutane's bioavailability.
- The sponsor clarified that they do not wish to label their product to be taken independent of food because this claim would require a clinical trial. FDA asked what would be the advantage of taking CIP-Isotretinoin in light of the safety concern.
- The sponsor clarified that the sources from which neuropsychiatric events were reported in the Hoffman La Roche comparative study included the patient diary, the investigator's questions, and the Beck inventory. Dr. Leydon questioned whether the reported difference in the number of neuropsychiatric events is real as he sees no difference between the two arms based on all the sources.
- There was some discussion about the possible study design of a head-to-head clinical safety trial comparing CIP-Isotretinoin to Accutane. FDA suggested using "real world" conditions (e.g., patients may or may not take isotretinoin with food; the standard high-fat meal is not used as the fed condition as this does not reflect the ordinary diet). Dr. Leydon suggested studying patients with mild acne as they are not as "psychologically wounded" as those with severe acne.

- The sponsor is willing to consider a postmarketing clinical safety study.

Action Items

- FDA will respond to the sponsor's position that a clinical safety study is not needed for approval of CIP-Isotretinoin as discussed in today's meeting.

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/s/

Julie Beitz
10/22/2007 01:50:40 PM



NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.
Attention: Larry Andrews, CEO and President, Cipher Pharmaceuticals, Ltd.
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Mr. Andrews:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10 mg, 20 mg, and 30 mg.

Your May 29, 2007 request for formal dispute resolution, received on May 29, 2007, concerned the Division of Dermatology and Dental Product's (DDDP's) decision to issue an approvable action for NDA 21-951 on April 25, 2007. DDDP determined that the NDA did not establish an adequate basis for the Agency to rely for approval of CIP-Isotretinoin Capsules upon its previous findings of safety for Accutane. Review of your appeal was deferred until after a post-action meeting was held with your firm and DDDP on June 27, 2007. On June 28, 2007, you resubmitted your original formal dispute resolution request, and requested a meeting with Drs. Robert Temple and Susan Walker, Ms. Elizabeth Dickinson from FDA's Office of Chief Counsel, and me. This meeting was held on July 11, 2007.

In your May 29, 2007 letter, you requested that I issue a decision stating that the safety of CIP-Isotretinoin, a new formulation of isotretinoin, has been established so that the application can move forward to approval. You indicated that this decision should be reached because the Agency has previously determined that Accutane is safe when taken as directed, i.e., under fed conditions at doses up to and including 2 mg/kg/day, and there is no suggestion in product labeling that one or more doses of Accutane should be taken fasted to reduce the chance of systemic toxicities. Since pharmacokinetic studies demonstrate that plasma levels of isotretinoin produced by CIP-Isotretinoin fall within the range of levels produced by Accutane under fed and fasted conditions, you have concluded that clinical studies are not needed to further demonstrate the safety of CIP-Isotretinoin relative to Accutane.

I have carefully reviewed your appeal as well as the administrative record for your original IND 64,927 and your NDA 21-951, including medical and clinical pharmacology reviews, meeting minutes, and the approvable letters dated May 1, 2006, and April 25, 2007. I have also reviewed publicly available documents related to other isotretinoin products (e.g., Sotret, Accutane NF) that the Agency has considered in the past. I have had extensive conversations with scientific staff in DDDP and the Office of Clinical Pharmacology (OCP). I attended CDER Regulatory Briefings on March 30, 2006,

and March 23, 2007, in which various aspects of this NDA were vetted.¹ I also attended meetings held with DDDP and your firm on March 13, 2006, and on June 27, 2007.

I have now completed my review. I have concluded that the statements you have made in your appeal regarding the dosing of Accutane as conveyed in product labeling and regarding isotretinoin plasma levels produced by CIP-Isotretinoin relative to Accutane are correct. However, I also conclude that the scientific and regulatory standards applied by DDDP are appropriate. I therefore concur with DDDP that clinical studies are needed to further demonstrate the safety of CIP-Isotretinoin relative to Accutane. This conclusion is based on the following considerations:

- 1) While CIP-Isotretinoin is bioequivalent to Accutane under fed conditions, it is not bioequivalent under fasted conditions;

The Agency and your firm are in agreement on this point.

- 2) The Agency has approved generic isotretinoin products in abbreviated new drug applications without requiring clinical safety and efficacy studies, however, these products have been demonstrated to be bioequivalent (as well as therapeutically equivalent) to the listed drug, Accutane, under both fed and fasted conditions;²

As you are well aware, CIP-Isotretinoin does not meet the bioequivalence standards for approval in an abbreviated new drug application.

- 3) We have experience that suggests that a difference in bioavailability of isotretinoin products under fasted conditions could be important. Like CIP-Isotretinoin, Hoffman LaRoche's proposed Accutane NF formulation produced isotretinoin plasma levels that fell within the range of levels produced by Accutane under fed and fasted conditions. A randomized controlled trial of Accutane NF vs. Accutane involving 600 patients demonstrated equivalent efficacy at the doses tested. However, the Agency's review identified safety concerns regarding the Accutane NF isotretinoin formulation. Compared with Accutane-treated patients, more patients treated with Accutane NF reported psychiatric adverse events (11 vs. 1), and more patients discontinued the study for psychiatric symptoms (4 vs. 0). No obvious explanation could be made for these findings,³ but it seems possible that the high fat meal effect seen in pharmacokinetic studies does not reflect the reality of taking drugs under actual use "fed" conditions (i.e., with a meal of different fat content). If plasma levels produced by Accutane NF exceeded those of Accutane under actual use "fed" conditions as might be seen in a clinical trial, a difference in safety profile might result.

Thus, given the safety concerns identified by the Agency in its review of another isotretinoin formulation that like CIP-Isotretinoin 1) produced plasma levels within the range of levels produced by Accutane under fed and fasted conditions, but 2) was not strictly bioequivalent to Accutane under both of these conditions, we are not prepared to assume that CIP-Isotretinoin will be comparable to

¹ The purpose of CDER Regulatory Briefings is to provide advice to staff on scientific and regulatory issues. They are not decisional meetings unless so stated. Neither of the Regulatory Briefings held to discuss NDA 21-951 were decisional.

² See e.g., FDA's review of bioequivalence studies submitted by Ranbaxy Pharmaceuticals, Inc. under ANDA 76-041 at <http://www.fda.gov/cder/foi/nda/2002/076041.pdf>; also conveyed in the Agency's minutes of the March 13, 2006 guidance meeting with DDDP.

³ See transcript from the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting held September 19, 2000, page pp. 273-277.

Accutane in terms of safety. Clinical studies would be needed to adequately characterize the safety profile of CIP-Isotretinoin prior to approval.

Additional Comments

I have reviewed the administrative record of your IND to ascertain what guidance DDDP provided to you during the clinical development of your product. Upon receipt of the original IND for CIP-Isotretinoin in June 2002, DDDP advised that pharmacokinetic studies alone may not be sufficient because “the impact of changes in drug absorption and elimination kinetics is unknown”. A phase 2 dose-ranging study was recommended followed by a large phase 3 study that included a comparable dose of Accutane as one of the treatment arms.⁴ At a guidance meeting on May 21, 2003, DDDP advised that if any of the dosage sizes were found to be more bioavailable than the same capsule size of Accutane, then clinical trials will be necessary.⁵ From my discussions with OCP, it is clear that pharmacokinetic studies have shown that CIP-Isotretinoin and Accutane produce similar half-life and clearance values for isotretinoin and its metabolites over the sampling period under fed conditions. In the Agency’s view, isotretinoin elimination following CIP-Isotretinoin administration has been adequately characterized and raises no concerns. However, CIP-Isotretinoin’s increased bioavailability under fasted conditions reflects its differential absorption from Accutane under these conditions, the impact of which is still unknown. Presumably the impact of this altered bioavailability would also manifest itself in a differential manner from that of Accutane under other dietary conditions that have not been formally studied (i.e., meals of different composition and/or volume).

At a subsequent guidance meeting on April 28, 2004, you indicated that you would not promote use of your product under fasted conditions, despite its increased bioavailability relative to Accutane under fasted conditions. DDDP advised that “any considerations that could be perceived as an advantage with the Cipher product should be demonstrated and proven clinically.”⁶ Your proposed labeling for CIP-Isotretinoin submitted with your May 29, 2007 letter states under CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption* tha

(b) (4)

This statement illustrates the inherent difficulty in describing the pharmacokinetic differences of CIP-Isotretinoin relative to Accutane without also implying claims of an advantage. Both less variable absorption between the fed and fasted states, and increased bioavailability under fasting conditions could potentially be viewed as advantageous. It also does not necessarily follow that a product that displayed such pharmacokinetic characteristics, as CIP-Isotretinoin does, would need to be administered with food.

Conclusions and Recommendations

The increase in plasma levels of currently marketed Accutane when taken with food (as opposed to under fasted conditions) is well known and has been described in the product label since approval in 1982. The DOSAGE AND ADMINISTRATION section of the Accutane label states, “Failure to take Accutane with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food instructions.” Unfortunately, there

⁴ See Agency’s fax dated June 25, 2002 regarding IND 64,927 submission 000.

⁵ See Agency’s minutes of the May 21, 2003 guidance meeting.

⁶ See Agency’s minutes of the April 28, 2004 guidance meeting.

is good reason to suspect that Accutane is not taken consistently with food,⁷ and that actual use “fed” conditions could have different implications depending on the exact nature of the food. In my view, a new isotretinoin formulation that was less dependent on food could represent an advance in the treatment of severe recalcitrant nodular acne.⁸ CIP-Isotretinoin may be that advance if it can be demonstrated to have a safety profile that is not substantially different from that of Accutane. It is possible, however, that the recommended dose for the product would differ from that of Accutane.

The bioequivalence studies performed to date with CIP-Isotretinoin evaluated too few patients for very short durations and were not properly designed to assess its overall safety profile relative to Accutane under conditions of use. I agree with DDDP’s recommendation that a prospective, randomized controlled study should be pursued to characterize CIP-Isotretinoin’s adverse event profile relative to Accutane. Such a study should be designed to detect psychiatric adverse events, among others. Given that depression is the most commonly reported adverse event associated with isotretinoin use in FDA’s Adverse Event Reporting System,⁹ symptoms of depression are likely to be observed in a randomized controlled trial. Characterization of their incidence, severity and associated adverse clinical outcomes would be important data to capture.

I would encourage you to work closely with the Division of Dermatology and Dental Products to develop a suitable prospective safety study of CIP-Isotretinoin. Request for review of the study protocol under a special protocol assessment is strongly recommended.

Alternatively, you could consider reformulating your product so that it meets bioequivalence standards for approval in an abbreviated new drug application as a generic product.¹⁰

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John Jenkins, Director of the Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent again through the Center’s Dispute Resolution Project Manager, Ms. Grace Carmouze. Any questions concerning your appeal should be addressed via Ms. Carmouze at 301-796-1654.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director, Office of Drug Evaluation III
Center for Drug Evaluation and Research

⁷ See transcript from the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting held September 19, 2000, page 243, in which Hoffman LaRoche’s survey of prescribing practices is described.

⁸ See minutes of a teleconference held with DDDP on January 16, 2005 which state “The Agency thinks that the drug provides no advantage and may possibly be a detriment to the public health.” My understanding of DDDP’s current position is that CIP-Isotretinoin’s lack of dependence on food could be viewed as advantageous if the product can be demonstrated to have a safety profile that is not substantially different from that of Accutane.

⁹ Data on file. Results from a search of FDA’s AERS database for isotretinoin-associated adverse events from approval to June 1, 2007.

¹⁰ Suggestion previously communicated to you in a 74-day letter from DDDP dated October 26, 2005

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/s/

Julie Beitz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.
ATTENTION: Larry Andrews, CEO and President, Cipher Pharmaceuticals, Ltd.
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Mr. Andrews:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin 10 mg, 20 mg, and 30 mg.

We also refer to the meeting between representatives of your firm and the FDA on July 11, 2007. The purpose of the meeting was to discuss your June 28, 2007 formal dispute resolution request.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1017.

Sincerely,

{See appended electronic signature page}

Maria R. Walsh, RN, MS
Project Management Officer
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 11, 2007
Time: 1:00 p.m. – 2:00 p.m.
Location: White Oak, Building 22, Conference Room 1311

Application: NDA 21-951: CIP-Isotretinoin Capsules
Type of Meeting: Formal Dispute Resolution

Meeting Chair: Julie G. Beitz, MD
Meeting Recorder: Maria R. Walsh, RN, MS

FDA Attendees:

Office of Drug Evaluation III

Julie G. Beitz, MD, Director
Maria R. Walsh, RN, MS, Project Management Officer
Division of Dermatology and Dental Products
Susan J. Walker MD, Director

Office of Medical Policy

Robert J. Temple, MD, Director

Office of Chief Counsel

Elizabeth H. Dickinson, Esq.

External Constituents Attendees:

Cipher Pharmaceuticals, Ltd.

Larry Andrews, CEO and President
Jason A. Gross, Pharm.D, VP Scientific Affairs
Julia Nash, Manager, Regulatory Affairs (via telephone)
Arthur Deboeck, Vice President, Galderma Pharmaceutical Research Inc., U.S. Agent for Cipher Pharmaceuticals (via telephone)

(b) (4)

Background: Cipher Pharmaceuticals submitted a formal dispute resolution request, dated June 28, 2007, to appeal the approvable action taken by the Division of Dermatology and Dental Products on NDA 21-951, CIP-Isotretinoin Capsules, 10mg, 20 mg, and 30 mg. The approvable letter, dated April 25, 2007, states, in part, that “the application did not establish an adequate basis for the Agency to rely on our previous finding of safety for the listed drug, Accutane,” because it did not demonstrate “that the difference in the pharmacokinetic profile of CIP-Isotretinoin as compared to Accutane is not clinically meaningful with regard to the safety profile of CIP-Isotretinoin.” The approvable letter includes the Division’s recommendation that the sponsor conduct a clinical trial in patients with severe recalcitrant nodular acne in which CIP-Isotretinoin is compared to Accutane at a dose of 1.0 mg/kg/day.

The sponsor's appeal included a request for a meeting with Dr. Julie Beitz, Dr. Robert Temple, Dr. Susan Walker, and Ms. Elizabeth Dickinson.

Meeting Summary:

Presentation

(b) (4) presented the following historical overview of and arguments for approval of NDA 21-951, CIP-Isotretinoin Capsules:

- Cipher Pharmaceutical's NDA for CIP-Isotretinoin Capsules was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act on June 27, 2005. It relies upon FDA's previous finding of safety and effectiveness for Hoffman LaRoche's Accutane (isotretinoin) Capsules and proposes the same indication as Accutane: treatment of severe recalcitrant nodular acne.
- Pharmacokinetic studies comparing systemic levels when both drugs were administered fed and fasted shows that CIP-Isotretinoin and Accutane are equivalent under fed conditions. The two drugs are not equivalent under fasted conditions but levels of CIP-Isotretinoin fasted fall in between the levels of Accutane fed and fasted (i.e. the relative bioavailability of CIP-Isotretinoin fasted is approximately 70% and that of Accutane fasted is approximately 40%).
- The April 25, 2007 approvable letter raises the question of whether the safety profile of CIP-Isotretinoin is the same as that of Accutane.
- FDA has made the determination that Accutane is safe under the conditions of use specified in the approved labeling which includes administration with a meal, retreatment, and upward titration to 2.0 mg/kg/day. According to the DOSAGE AND ADMINISTRATION section of the approved labeling:
 - Accutane should be administered with a meal (this recommendation is also reinforced in the PRECAUTIONS section and the MEDICATION GUIDE);
 - All doses studied (0.1, 0.5, and 1.0 mg/kg/day) provided initial clearing of disease, but there was a greater need for retreatment with the lower dosages;
 - Dose adjustments up to 2.0 mg/kg/day may be made in severe cases if tolerated but patients should be questioned about their compliance with food instruction before upward dose adjustments are made;
 - A second course of therapy may be initiated if warranted by persistent or recurring severe nodular acne.
- FDA addressed the risk of teratogenicity by approving the S.M.A.R.T. risk management program and subsequently the iPLEDGE risk management program under Subpart H (accelerated approval for serious or life-threatening illnesses).

FDA addressed neuropsychiatric adverse events by approving extensive revisions to the WARNINGS section of the labeling that includes a recommendation that patients should stop taking Accutane if they develop depression or other neuropsychiatric adverse events.

- FDA's safety determination is based on Accutane when taken fed. Nothing in the approved labeling suggests that the approved fed doses are not safe or that dose relationships play a role in the development of adverse events such that patients should periodically miss doses or occasionally take the drug fasted or that physicians should titrate the dose down.

On the contrary, the approved labeling suggests that the dose may be titrated up to avoid retreatment and that patients should take Accutane with a meal. FDA has repeatedly approved labeling supplements for Accutane reaffirming its determination that Accutane is safe under these specified conditions of use.

- Cipher Pharmaceuticals is entitled to rely on FDA's previous finding of safety for Accutane. Since pharmacokinetic studies demonstrate that the levels of isotretinoin produced by CIP-Isotretinoin are within the range of levels produced by Accutane, CIP-Isotretinoin should be approved.

Discussion

- The sponsor clarified that the possibility of conducting a phase 3 study was discussed with FDA during development in the context of submitting a 505(b)(2) application that demonstrates an advantage over Accutane with regard to a different pharmacokinetic profile and dosing schedule.
- FDA noted that the pharmacokinetic trials comparing CIP-Isotretinoin and Accutane under fed conditions were conducted using a high fat meal. FDA commented that since the difference in CIP-Isotretinoin blood levels between fed and fasted conditions (30%) is less than that of Accutane (60%), even if both products are taken with food during ordinary use, blood levels of CIP-Isotretinoin are likely to be higher than those of Accutane in the presence of a normal diet during ordinary use. The impact of this difference on safety is unknown.
- FDA said that a large percentage of adolescents do not take Accutane with a meal as recommended in the labeling. Therefore, during ordinary use, patients taking CIP-Isotretinoin would be exposed to a higher level of isotretinoin than patients taking Accutane. FDA is concerned about emerging post-marketing safety issues including systemic toxicities and potential neuropsychiatric events. Since the relationship between dose and adverse events is unknown, the safety profile of CIP-Isotretinoin may differ from that of Accutane. Therefore, additional safety data is needed before CIP-Isotretinoin may be approved.
- The sponsor said that FDA has determined that Accutane is safe when used under the conditions of use specified in the approved labeling including the recommendation that Accutane be taken with a meal. Although it is usual to be concerned about dose response and adverse events, the Accutane labeling actually recommends increasing the dose to avoid retreatment. As a 505(b)(2) application, the sponsor is entitled to rely on FDA's previous finding of safety for Accutane as reflected in the approved labeling.
- FDA pointed out that unlike a generic drug submitted under an ANDA, CIP-Isotretinoin is different than Accutane. FDA's previous finding of safety for Accutane was based on

Accutane's characteristics and FDA needs to determine if CIP-Isotretinoin's difference with Accutane impacts safety. FDA cannot ignore emerging safety issues just because an NDA is submitted pursuant to 505(b)(2).

- FDA said a similar product, Hoffman La Roche's Accutane NF, was discussed at an Advisory Committee meeting on September 18, 2000. Systemic levels of Accutane NF, both fed and fasted, fall in between those of Accutane (i.e. Accutane NF fed is 50% lower than Accutane fed and 15-20% higher fasted than Accutane fasted). In the clinical trials comparing the two products, an increased number of neuropsychiatric events were observed in patients who took Accutane NF as compared to patients who took Accutane. This occurrence raises the possibility that differences in pharmacokinetic profiles can impact safety.
- The sponsor said that CIP-Isotretinoin differs from Accutane NF in that Accutane NF is an extended release product intended for once daily dosing with or without food whereas CIP-Isotretinoin is not an extended release product, is intended to be administered the same as Accutane (i.e. twice daily with food), and has the same pharmacokinetic profile of Accutane fed dose for dose.

Action Items

- Dr. Beitz will respond to the sponsor's formal dispute resolution request within 30 days after this meeting.

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/s/

Maria Walsh

8/9/2007 12:34:08 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.
Attention: Larry Andrews, CEO and President, Cipher Pharmaceuticals, Ltd.
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Mr. Andrews:

Please refer to your New Drug Application (NDA) submitted under section 5-5(b)(2) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10mg, 20mg, and 30mg.

We also refer to the meeting between representatives of your firm and the FDA on June 27, 2007. The purpose of the meeting was to discuss a pathway forward for this application.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Melinda Bauerline, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Susan Walker, M.D.
Division Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 27, 2007
TIME: 11:00am to 11:45am
LOCATION: White Oak, Building 22, Room 1311
APPLICATION: NDA 21-951
DRUG NAME: CIP-Isotretinoin
TYPE OF MEETING: Type A, Post-Action

MEETING CHAIR: Susan Walker, M.D.

MEETING RECORDER: Margaret Kober, R.Ph., M.P.A.

FDA ATTENDEES:

Julie Beitz, M.D., Director, Office of Drug Evaluation III
Susan Walker, M.D., Director, Division of Dermatology and Dental Products (DDDP)
Stanka Kukich, M.D., Deputy Director, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Denise Cook, M.D., Medical Reviewer, DDDP
Dennis Bashaw, Pharm.D., Director, Division of Clinical Pharmacology III
Margaret Kober, R.Ph., M.P.A., Acting Chief, Project Management Staff, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

Larry Andrews, CEO and President, Cipher Pharmaceuticals, Ltd. (Cipher)
Jason A Gross, Pharm.D., Vice President, Scientific Affairs, Cipher
Julia Nash, Manager, Regulatory Affairs, Cipher

(b) (4)

BACKGROUND:

NDA 21-951 was submitted June 27, 2005, as a 505(b)(2) application. An approvable letter was sent to the sponsor on May 1, 2006. The approvable letter cited, among other deficiencies, the increased bioavailability of CIP-Isotretinoin compared to the referenced listed drug, Accutane (isotretinoin capsules), precluding the reliance on our previous finding of safety and effectiveness for Accutane as the sole basis of approval for CIP-Isotretinoin. The sponsor submitted a complete response to the original approvable letter on October 26, 2006. A second approvable letter was sent to the sponsor on April 25, 2007. This letter cited a chemistry deficiency and the lack of an adequate basis to rely on a finding of safety for the referenced listed drug.

MEETING OBJECTIVE:

To determine a pathway forward for this application.

DISCUSSION POINTS:

1. Dr. Beitz was in attendance for information-gathering purposes only.
2. The sponsor reiterated the material provided in the meeting package to justify why the application could be approved, as is, based on 505(b)(2) criteria.
3. The Agency clarified the position that the information provided in Cipher's application was insufficient to allow reliance on a previous finding of safety and effectiveness for the referenced listed drug because the two products were not bioequivalent and, therefore, additional information was needed to bridge this gap.
4. The sponsor may either choose to provide the additional information in the form of a resubmission or pursue Formal Dispute Resolution.

ACTION ITEMS:

Minutes will be provided to the sponsor within 30 days.

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/s/

Susan Walker

7/24/2007 01:33:44 PM



NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.
ATTENTION: Larry Andrews, CEO and President, Cipher Pharmaceuticals, Ltd.
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Mr. Andrews:

We refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10 mg, 20 mg, and 30 mg.

We refer also to your June 28, 2007, request for formal dispute resolution received on June 29, 2007. The appeal concerns the Division of Dermatology and Dental Products' decision not to approve NDA 21-951 as reflected in the approvable letter dated April 25, 2007.

Your formal dispute resolution request also included a request for a meeting to discuss the issues described in the appeal document. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000) The meeting is scheduled for:

Date: July 11, 2007

Time: 1:00 - 2:00 pm

Location: White Oak, Building 22, Room 1311

CDER participants:

Julie Beitz, MD, Director, ODE III

Robert Temple, MD, Director, Office of Medical Policy

Susan Walker, MD, Director, Division of Dermatology and Dental Products

Elizabeth Dickinson, Esq., Office of Chief Counsel

Maria R. Walsh, RN, MS, Project Management Officer, ODE III

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, e-mail that information to Maria R. Walsh at maria.walsh@fda.hhs.gov so that we can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards the following telephone number to request an escort to the conference room: Maria R. Walsh, (301) 796-1017.

We will respond to the appeal within 30 days after the meeting.

NDA 21-951

Page 2

If you have any questions, call Maria R. Walsh, Project Management Officer, at (301) 796-1017.

Sincerely,

{See appended electronic signature page}

Grace Carmouze
Lead Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Grace Carmouze

7/5/2007 03:23:39 PM



NDA 21-951

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.
ATTENTION: Arthur Deboeck, Vice President and General Manager
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Mr. Deboeck:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10, 20, and 30mg..

We refer also to your May 29, 2007, request for formal dispute resolution received on May 29, 2007. The appeal concerned the need to conduct a clinical trial in patients with severe, recalcitrant nodular acne in which CIP-Isotretinoin is compared to Accutane at a dose of 1.0 mg/kg/day to establish an adequate safety profile of your product. Your submission included a request for a meeting with the Director of the Office of Drug Evaluation III and other FDA personnel to resolve this dispute.

As discussed with you on June 1, 2007, it would be inappropriate to consider this matter under formal dispute resolution at this time. Your arguments regarding the issues raised in the April 25, 2007, approvable letter have not been presented fully to the Division of Dermatology and Dental Products in accordance with the procedures for dispute resolution described in 21 CFR 314.103 and the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level". If, after a meeting with the Division, the issue is still not resolved to your satisfaction, you may appeal the matter to the Director of the Office of Drug Evaluation III.

If you have any questions regarding the formal dispute resolution process, please contact Grace Carmouze, Formal Dispute Resolution Project Manager, at (301) 796-1654. If you have any questions regarding the application, please contact Melinda Bauerlien, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Grace Carmouze
Formal Dispute Resolution Project Manager
Lead Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Grace Carmouze

6/4/2007 10:43:32 AM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: March 21, 2007

To: Mr. Arthur Deboeck	From: Victoria Lutwak for Melinda Bauerlien
Company: Cipher Pharmaceuticals Limited U.S. Agent	Division of Dermatology and Dental Products
Fax number: 301 560-6640	Fax number: 310-796-9894/ 95
Phone number: 787- 713-0304	Phone number: (301) 796-2445
Subject: NDA 21-951	

Total no. of pages including cover: 1

Comments: We have the following request for information:

Please clarify why there is imbalance in reported neuro-psychiatric events between study 666 and study 442.

We would like a response by close of business Thursday, March 22nd. If this is not possible, please let me know. Thank you. Vickey Lutwak

Document to be mailed: YES NO

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/s/

Victoria Lutwak
3/21/2007 01:45:49 PM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: March 6, 2007

To: Arthur Deboueck	From: Melinda Bauerlien, M.S. Project Manager
Company: Galephar for Cipher Pharmaceuticals	Division of Dermatologic & Dental Drug Products
Fax number: (301) 560-6640	Fax number: (301) 796-9895
Phone number:	Phone number: (301) 796-2110
Subject: NDA 21-951	

Total no. of pages including cover: 2

Comments: Request for information

Please send in all CRFs for patients in the studies that comprise this submission. To expedite this, send in ASAP the CRFs of all patients who experienced an adverse event during the trials.

Document to be mailed: YES NO

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/s/

Melinda Bauerlien
3/6/2007 01:26:48 PM
CSO



NDA 21-951

INFORMATION REQUEST LETTER

Galephar P.R., Inc. for Cipher Pharmaceuticals, Ltd.
Attention: Arthur DeBoeck, Vice President and General Manager
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Mr. Deboeck:

Please refer to your June 27, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules 10, 20, and 30 mg.

We also refer to your submission dated October 26, 2006, which was a complete response to our action letter dated May 1, 2006.

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

1. Note that “Immediate-Release Dosage Forms which requires that an amount (b) (4)” of the active be delivered at the end of the test” is only for true Immediate-Release (IR) dosage forms.

Under general monograph USP <1088> “In- Vitro and In-vivo Evaluation of Dosage Forms”, the testing time for IR dosage forms is generally 30 to 60 minutes with a single time point specification.

FDA guidance for industry “Waiver of In-Vivo Bioavailability and Bioequivalence Studies for IR Solid Dosage Forms Based on a Biopharmaceutics Classification System” August 2000, section II.C. under Dissolution, also states that “an IR drug product is considered *rapidly dissolving* when no less than (b) (4) of the labeled amount of the drug substance dissolved with in 30 minutes, using USP apparatus I at 100 rpm (or USP apparatus II at 50 rpm) in a volume 900mL or less in each of the following media: (1) 0.1 HCl or stimulated gastric fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP with out enzymes”.

In an article “Overview of Workshop: In vitro dissolution of IR Dosage forms: Development of in vivo Relevance and Quality Control Issues” (Drug Information Journal, Vol. 30, pp 1029 – 1037, 1996), Dr. McClintock has stated “The regulatory agencies expect the USP apparatus to be applied, and for IR dosage forms, a Q value of (b) (4) dissolved with in an hour”.

Based on above references, CIP-Isotretinoin capsule is not deemed as an IR dosage form. Moreover, we want to assure that there is no early dose dumping of the drug substance in the proposed drug product by monitoring the dissolution profile. Furthermore, the dissolution profile will be instrumental for qualifying post approval changes through similarity (f_2) calculation.

Therefore, we reiterate our recommendation to establish multiple time points (minimum of 30, 60, 120, 180 and 240 minutes) based on typical dissolution profile for the product to set the acceptance criteria on for each time point as well as minimum released at the end of the test. These changes should be implemented in the revised release as well as stability specifications.

2. Provide the following analysis of the two dose proportionality studies contained in the NDA resubmission:
 - a. An analysis of mean absorption time/mean residence time for each treatment. This analysis should include both descriptive statistics (mean, median, std. dev, %CV, etc.) as well as a graphical display (i.e. a box whisker plot) of the individual data by treatment.
 - b. Individual and mean Wagner-Nelson plots of the data for each treatment in these two studies. Where appropriate, the multi-compartment correction for W-N should be used. The resulting data should be displayed as both individual plots and an overall mean plot of the results for each treatment. In addition, the data for each treatment should also be summarized on a single plot with all subjects displayed so that the overall trend can be more readily examined.

If you have any questions, call Melinda Bauerlien, M.S., Project Manager, at 301-796-2110.

Sincerely,

See appended electronic signature page

Susan Walker, M.D.
Division Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Stanka Kukich
2/12/2007 02:14:05 PM
Sign off for Susan Walker, Division Director



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-951

Galephar P.R. Inc. for Cipher Pharmaceuticals, Ltd.
Attention: Arthur Deboeck, Vice President and General Manager
Road 198 km 14.7 #100
Juncos Industrial Park
Juncos 00777-3873, Puerto Rico

Dear Mr. Deboeck:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules for severe recalcitrant nodular acne.

We also refer to the meeting between representatives of your firm and the FDA on March 13, 2006. The purpose of the meeting was to discuss the sponsor's response to the Agency's 74 Day Filing Letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Acting Division Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: March 13, 2006 **Time:** 3:00 P.M.

Location: WO1313 **Meeting ID:** 17026

Topic: NDA 21-951, CIP-Isotretinoin Capsules for severe recalcitrant nodular acne

Subject: Guidance Meeting

Sponsor: Cipher Pharmaceuticals, Ltd.

Meeting Chair: Stanka Kukich, M.D./Acting Division Director, DDDP, HFD-540

Meeting Recorder: Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDP, HFD-540

FDA Attendees:

Stanka Kukich, M.D./Acting Division Director, DDDP, HFD-540
Julie Beitz, M.D./Acting Director, ODE III, HFD-103
Bronwyn Collier/Associate Director for Regulatory Affairs, ODE III, HFD-103
Elizabeth Dickinson/Attorney, OCC, GCF-1
Elaine Tseng/Regulatory Counsel, ORP, HFD-7
Kim Colangelo/Associate Director for Regulatory Affairs
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology, DDDP, HFD-540
Denise Cook, M.D./Clinical Reviewer, DDDP, HFD-540
Dennis Bashaw, Pharm.D./Team Leader, Clinical Pharmacology, DCPIII, HFD-880
Ameeta Parekh, Ph.D./Pharmacologist, DCPIII, HFD-880, OND
Donald Hare, Pharm.D./Special Assistant to the Director, OGD, HFD-604
Mary Jean Kozma-Fornaro/Chief, Project Management Staff, DDDP, HFD-540
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDP, HFD-540

Sponsor Attendees:

Cipher Pharmaceuticals, Ltd.

Larry Andrews/President



Arthur Deboeck/Vice President and General Manager, Galephar PR, Inc.

Purpose:

To discuss issues raised in the Agency's 74-Day Filing Letter.

The sponsor opened the meeting by asking the Agency if they have satisfied the safety issues proposed by the Agency in the 74-Day Filing Letter dated October 26, 2005.

The Agency responded that under the 505(b)(2) rubric, the sponsor must demonstrate that it is scientifically appropriate for the proposed drug product to rely for approval on the agency's finding of safety and effectiveness for the reference product by performing a comparative bioavailability study, in this case Accutane™. While there is no requirement, under 505(b)(2) for their product to be "bioequivalent" to the reference product, bioequivalence does establish the most persuasive link to the clinical efficacy and safety data supporting the approval of the referenced drug. Should the levels of the proposed drug fall either above or below those for the reference product, then new in vivo clinical trials may be necessary to establish that the proposed product will be safe and effective for the proposed conditions of use.

The sponsor stated that under fed conditions their 10 and 40 mg doses were bioequivalent to Accutane™.

With regards to the general nature of the pharmacokinetic section of this NDA, there is still ongoing concern regarding the use of fed comparisons. As has been noted previously and communicated to the sponsor on multiple occasions, bioequivalence/bioavailability studies are normally done in fasted state. The Agency acknowledges the sponsor's contention that the Accutane™ label does indicate that doses should be taken with food, however, it is our opinion that the homogenizing effects of food are to generally be avoided in establishing "bio-bridges". We note that the Office of Generic Drugs requires that all of the currently approved Accutane™ generics demonstrate both Fed and Fasted bioequivalency. The Agency also notes that findings of bioequivalence encompass rate as well as extent.

The sponsor responded that the studies they conducted included head-to-head PK studies with their 10, 20mg strengths vs. 10 and 20mg strengths of Accutane™ and dose adjusted comparisons between their 30mg capsule and Accutane's™ 40 mg strength.

While the sponsor has done these head to head PK comparisons, they have not demonstrated dose proportionality across their range of dosage units. The one study they have done in this area not only failed to demonstrate dose proportionality, but failed in such a way that the data was not consistent (some values high, some values low, not tied to dosage strength). The Agency is concerned that the lack of a true demonstration of dose proportionality will not allow them to make appropriate dosing suggestions in the label. Ultimately, while the sponsor can and has shown some degree of similarity between the Cipher product and Accutane™, with a 505(b)2, the question is, is it close enough to be able to rely on the agency's finding of safety and effectiveness for Accutane™, and to ensure a similar degree of clinical safety and efficacy?

The sponsor stated that doctors start dosing at a lower level and increase until it works. The side effects are not dose linked. Further, the sponsor stated CIP is not proposed to be AB rated so there should not be a risk of CIP being given instead of Accutane™. The amount the patient absorbs would at most double, which is still within the range of Accutane™. The sponsor also

stated that they have data on dosage vs. side effects with Accutane™. CIP is tied closely to Accutane™ for safety and efficacy. The sponsor stated that they will provide more literature to back up their conclusion. They do not want to conduct another clinical trial.

The Agency responded that the sponsor should submit the literature along with supportive data for review to support their assertions of safety and efficacy of their drug to the NDA. Literature by itself may not be sufficient evidence of clinical safety and effectiveness without primary data for evaluation.

Addendum:

Depending on the extent of the new information being submitted to the NDA, the review clock may be extended.

Minutes Preparer: _____
Melinda Harris-Bauerlien, M.S./Regulatory Project Manager, DDDP, HFD-540

Chair Concurrence: _____
Stanka Kukich, M.D./Acting Division Director, DDDP, HFD-540

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/s/

Stanka Kukich

4/4/2006 01:56:58 PM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: January 24, 2006

To: Arthur Deboueck	From: Melinda Harris-Bauerlien, M.S. Project Manager
Company: Galephar for Cipher Pharmaceuticals	Division of Dermatologic & Dental Drug Products
Fax number: (787) 713-0344	Fax number: (301) 796-9895
Phone number: (787) 713-0340	Phone number: (301) 796-2110
Subject: NDA 21-951	

Total no. of pages including cover: 3

Comments: Clinical Pharmacology request for information. Please respond by 2/2/06.

Document to be mailed: YES NO

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ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
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received this document in error, please notify us immediately by telephone at (301) 827-
2020. Thank you.**

While acknowledging that pooled study results were requested in the Dec. submission and provided, the within study results for 441 and 442 have not been provided, as was done for 627 and 727, etc. For example, in study 441, the AUCinf, Cmax, Tmax and Kel for the three treatments in the study (Cipher fed, Accutane fed and fasted) should be on one box whisker plot for each parameter without data from other studies. As the objective of 441 was relative BA between the Cipher product and a comparison of the Accutane data, the plots provided should reflect that, along with the cross study comparison of the data that has been previously provided.

Difficulty has been encountered in the organization and formatting of the SAS transport files as supplied. The ones submitted for study 441, 443, and 444 are not usable in their current format. As the jumbled nature of the data file has necessitated a fair degree of data entry by this reviewer as part of their analysis, additional plots will need to be generated by the sponsor. Specifically, plasma concentration-time profiles for all subjects on a treatment, on a single plot per treatment, should be generated on a 0-24hr time scale (truncating the post-24hr samples for studies 627,666, 727, and 734.

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/s/

Melinda Harris-Bauerlien
1/24/2006 07:56:52 AM
CSO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 15, 2005

BACKGROUND: NDA 21-951 for CIP-Isotretinoin Capsules is a 505(b)2 application providing for a change in dosage strengths from the Reference Listed Drug, Accutane (NDA 18-662 isotretinoin) from 10, 20 and 40 mg to 10, 20, and 30 mg.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an (b) (4) formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Jonathan Wilkin, M.D.; Denise Cook, M.D.; Jill Lindstrom, M.D.; Jiaquin Yao, Ph.D.; Paul Brown, Ph.D.; Steve Hathaway, Ph.D.; Ramesh Sood, Ph.D.; Dennis Bashaw, Pharm.D.; Donald Hare; Mary Jean Kozma-Fornaro, Melinda Harris-Bauerlien, M.S.

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

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Denise Cook/Jill Lindstrom (TL)
Secondary Medical:	N/A
Statistical:	N/A
Pharmacology:	Jiaquin Yao/ Paul Brown (Supervisor)
Statistical Pharmacology:	N/A
Chemistry:	Steve Hathaway/Ramesh Sood (TL)
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Dennis Bashaw
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	Melinda Harris-Bauerlien
Other Consults:	N/A

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain:

CLINICAL FILE 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	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input type="checkbox"/>	REFUSE TO FILE <input checked="" type="checkbox"/>

- Biopharm. inspection needed? YES NO
- PHARMACOLOGY N/A FILE REFUSE TO FILE
- GLP inspection needed? YES NO
- CHEMISTRY FILE REFUSE TO FILE
- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments: N/A

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

- The application is unsuitable for filing. Explain why: This application seeks approval for a product that is a duplicate of Accutane (NDA 18-662) (i.e., same active ingredient, dosage form, range of strengths, route of administration, and labeling). It is therefore eligible for submission under section 505(j). Since you neither claim nor identify a clinically relevant difference between your product and the reference listed product, your drug product appears to be unintentionally more bioavailable than the listed drug when dosed in a fasted state. The clinical significance of this difference, if any, is unknown and is not described in the proposed labeling.

Due to an administrative error with regard to the filing date, the application was technically filed (Filing Date - August 30, 2005) regardless of the fact that the Refuse to File Letter (issued August 31, 2005) had been sent to the applicant.

- 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.
 - 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.

Melinda Harris-Bauerlien, M.S.
Regulatory Project Manager, HFD-540

Stanka Kukich, M.D.
Acting Division Director, HFD-540

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Accutane, NDA 18-662 (isotretinoin)

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a change in dosage strengths from 10, 20, and 40 mg to 10, 20 and 30 mg.
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

The issuance of the Refuse to File letter on August 31, 2005, was missed by 1 day. Therefore the application was filed on August 30, 2005.

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

See #7

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
YES NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 64,927 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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/s/

Melinda Harris-Bauerlien
1/3/2006 09:12:20 AM
CSO

Stanka Kukich
1/3/2006 11:02:49 AM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-951 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: CIP
Established Name: Isotretinoin Capsules
Strengths: 10, 20, and 30 mg

Applicant: Cipher Pharmaceuticals, Ltd.
Agent for Applicant: Galephar P.R, Inc.

Date of Application: June 27, 2005
Date of Receipt: July 1, 2005
Date clock started after UN: N/A
Date of Filing Meeting: August 15, 2005
Filing Date: August 30, 2005
Action Goal Date (optional): May 1, 2006 User Fee Goal Date: May 1, 2006

Indication(s) requested: severe recalcitrant nodular acne

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: pediatric exclusivity expires in November 2005
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign. **Has been requested.**
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain: No statistical section was included.
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? N/A

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification. **Has been requested.**

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 64,927
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic “Content of Labeling” submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

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/s/

Melinda Harris-Bauerlien
12/28/2005 10:28:18 AM
CSO

Mary Jean Kozma Fornaro
12/28/2005 10:55:18 AM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: December 8, 2005

To: Arthur Debouek	From: Melinda Harris-Bauerlien, M.S. Project Manager
Company: Galephar for Cipher Pharmaceuticals	Division of Dermatologic & Dental Drug Products
Fax number: (787) 713-0344	Fax number: (301) 796-9895
Phone number: (787) 713-0340	Phone number: (301) 796-2110
Subject: NDA 21-951	

Total no. of pages including cover: 3

Comments: Response to your submission dated November 2, 2005

Document to be mailed: YES NO

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other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at (301) 827-
2020. Thank you.**

NDA 21-951 Response to sponsor's submission dated November 2, 2005

In regards to your question, in item 1 we had noted that they had provided the data in SAS transport files, but the figures, and text portion of the reports in the NDA were not provided electronically. In item 1 we were inquiring as to the availability of this information in an electronic form, ie. MS-Word files. In their response they indicated that they have both PDF and MS-Word files available for different portions of the document. For the purposes of the review we would like to receive the MS-Word files that are available for the narrative portion for all of the pk studies in the NDA. The rendered PDF files are not needed at this time, however, selected portions may be requested on an as needed basis.

Also the intention of item 3 was not to provide the sponsor with a comprehensive list of "clipped" tables in the NDA but to alert them to the fact that this issue had arose and that they should examine their data integrity.

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/s/

Melinda Harris-Bauerlien
12/8/2005 09:20:36 AM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: November 14, 2005

To: Arthur Deboueck	From: Melinda Harris-Bauerlien, M.S. Project Manager
Company: Galephar for Cipher Pharmaceuticals	Division of Dermatology & Dental Products
Fax number: (787) 713-0344	Fax number: (301) 796-9895
Phone number: (787) 713-0340	Phone number: (301) 796-2110
Subject: NDA 21-951 Request for Information	

Total no. of pages including cover:

Comments: Request for Information. Please provide as soon as possible.

Document to be mailed: YES NO

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other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at (301) 827-
2020. Thank you.**

NDA 21-951 Request for Information

Please provide the following:

1. A 356h with the signature of the U.S. agent.
2. A debarment certification signed by Cipher Pharmaceuticals.

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/s/

Melinda Harris-Bauerlien
11/14/2005 01:54:03 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-951

Cipher Pharmaceuticals, Limited
Attention: Larry Andrews, President
409 Matheson Blvd.
E. Mississauga, ON Canada L4Z 2H2

Dear Mr. Andrews:

Please refer to your June 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP-Isotretinoin Capsules

Your application was determined to not be fileable with the RTF letter issued August 31, 2005. Because of an administrative date calculation error, the notification of the application being not fileable was issued one day beyond the filing date. Therefore, the application was technically filed under section 505(b) of the Act on August 30, 2005, in accordance with 21 CFR 314.101(a).

We provide the following preliminary review comments.

You neither claim nor identify a clinically relevant difference between your product and the reference listed product even though your product fails to achieve bioequivalence and hence fails to meet criteria for a generic product.

Furthermore, you have not conducted a clinical study to support your claim of no difference. Even if you conducted a clinical study and demonstrated no clinically relevant differences in safety and efficacy between your product and the reference listed product, the 505(b) (2) pathway is not an appropriate pathway to pursue since you will not have shown any advantage for your product. In general, we do not approve 505(b) (2) applications for bioinequivalent products unless the difference is intentional and serves some clinical purpose, such as controlled release. More consistent bioavailability might be shown to represent such an advantage but you have not demonstrated that.

We are also concerned that patients titrated on the reference listed product who are switched to your product might, if they take your product in the fasted state, experience sharp increases in blood levels. You have not addressed this issue.

We suggest that you consider reformulating your product so that it meets bioequivalence standards for a generic product.

We are providing the above comments to give you preliminary notice of potential review issues. A formal response to these comments is not expected but will be reviewed if submitted in a timely manner. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. In the NDA, the pharmacokinetic (PK) data are available in SAS transport files. Please submit an electronic copy of the report itself.
2. An examination of the study reports indicate that while some of the studies did have significant female representation, a gender based analysis of the PK of isotretinoin does not appear to have been conducted. Please provide such an analysis for those studies where there was a significant female representation.
3. Throughout the NDA a number of the summary tables have been "clipped"(i.e., the printed results are truncated). As an example, but by no means an exhaustive list:

Module 2, vol. 2, 2.7.1, page 32, the 90% CI's are clipped

Module 2, vol. 2, 2.7.1, page 49 again the 90% CI's are clipped

The sponsor should review their tables and make updates as appropriate.

4. For isotretinoin and tretinoin, to aide in recognition of the variability in PK parameters across the studies, please provide a summary box whisker plot for the PK data across the studies, for example, C_{max} for equivalent doses, at equivalent days across the studies, on one figure. Similar figures should be prepared for AUC, K_{el} , $t_{1/2}$ and other relevant parameters.

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

If you have any questions, call Melinda Harris-Bauerlien, M.S., Regulatory Project Manager, at (301) 796-0906

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Acting Division Director
Division of Dermatology & Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Stanka Kukich
10/26/2005 08:24:59 AM



NDA 21-951
Cipher Pharmaceuticals Limited
Attention: Larry Andrews
Chairman & Chief Scientific Officer
409 Matheson Blvd.
E. Mississauga, ON Canada L4Z 2H2

Dear Mr. Andrews:

Please refer to your new drug application(s) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIP – Isotretinoin Capsules 10 mg, 20 mg, and 30 mg.

We also refer to the September 19, 2005, teleconference between [REDACTED] ^{(b) (4)} regulatory Consultant for the sponsor, Jonathan Wilkin, M.D. Division Director of the Division of Dermatologic and Dental Drug Products and Melinda Harris-Bauerlien, M.S., Project Manager.

Due to an administrative error, the Refuse to File letter for the above referenced NDA was sent a day following the 60 day filing date. Therefore, the NDA has been filed and will be reviewed under a 10 month review clock. The sponsor will receive a 74 day letter outlining any review issues for the NDA.

If you have any questions, call Melinda Harris-Bauerlien, M.S. Project Manger, at 301-796-2110.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Stanka Kukich
10/4/2005 08:58:15 AM
sign off for Dr. Wilkin, Division Director



NDA 21-951

Cipher Pharmaceuticals Ltd.
Attention: Larry Andrews, President
409 Matheson Blvd.
E. Mississauga, Ontario
Canada L4Z 2H2

Dear Mr. Andrews:

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: CIP-Isotretinoin Capsules

Review Priority Classification: Standard (S)

Date of Application: June 27, 2005

Date of Receipt: July 1, 2005

Our Reference Number: NDA 21-951

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 August 30, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 1, 2006.

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 requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-951

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs, HFD-540
Attention: Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Melinda Harris-Bauerlien, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Melinda Harris-Bauerlien
7/12/05 02:09:34 PM
Signed for Mary Jean Kozma-Fornaro