

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022370Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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

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

NDA NUMBER

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 (OR PROPOSED TRADE NAME)
CIP-TRAMADOL ER CAPSULES

ACTIVE INGREDIENT(S)
Tramadol hydrochloride

STRENGTH(S)
100, 200 and 300 mg

DOSAGE FORM
Oral

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

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

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

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

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

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

Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

J. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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

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

Date Signed
4/14/2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Jason A. Gross, Pharm.D., Vice President, Scientific Affairs

Address

Cipher Pharmaceuticals Incorporated
5650 Tomken Road, Unit 16

City/State

Mississauga, Ontario
Canada

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

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

1.3.1.2 Patent Certification

There are two Reference Listed Drugs (RLDs) for this application, and the following patent-related documentation is provided:

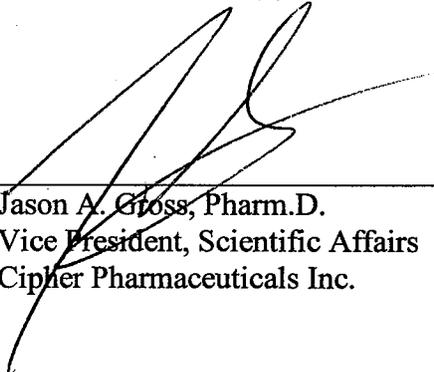
- ULTRAM® ER (tramadol HCl) Extended-Release Tablets - A Paragraph III Certification to the only listed patent.
- ULTRAM® (tramadol hydrochloride tablets) - A Method-of-Use Patent Statement.

**PATENT CERTIFICATION
ULTRAM® ER**

**Paragraph III Certification
U.S. Patent No. 6,254,887**

In accordance with the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended September 24, 1984, and December 8, 2003, a Patent Certification as to U.S. Patent No. 6,254,887 ("the '887 patent") is hereby provided for the New Drug Application ("NDA") for CIP-Tramadol Hydrochloride Extended-Release Capsules 100 mg, 200 mg and 300 mg.

Cipher Pharmaceuticals Inc. ("Cipher") hereby certifies that, according to FDA's electronic Orange Book, the '887 patent is set to expire on or about May 10, 2014. Cipher does not seek approval of its NDA before the expiration of this patent. This certification is made in accordance with Section 505(b)(2)(A)(iii) of the FFDCA, 21 U.S.C. § 355(b)(2)(A)(iii), and 21 C.F.R. § 314.50(i)(1)(i)(A)(3).



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

April 14, 2008
Date

**Method-of-Use Patent Statement
ULTRAM®**

U.S. Patent No. 6,339,105

As required by Section 505(b)(2)(B) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(b)(2)(B), as amended September 24, 1984 and December 8, 2003, and 21 C.F.R. § 314.50(i)(1)(iii), Cipher Pharmaceuticals Ltd. hereby states that the method-of-use patent, U.S. Patent No. 6,339,105 (“the ‘105 patent”), set to expire on or about October 12, 2019 (with pediatric exclusivity extending until April 12, 2020) according to FDA’s electronic Orange Book, does not claim a use for which Cipher is seeking approval for its CIP-Tramadol ER Capsules 100, 200, and 300 mg.

Name	Patent Number	Use Code	Expiry Date
ULTRAM® (tramadol hydrochloride tablets)	6,339,105	U-435	October 12, 2019

According to FDA’s electronic Orange Book, the ‘105 patent and U-435 use code are limited to “a titration dosing regimen for the treatment of pain using an initial dose of about 25 mg.” Cipher’s proposed labeling does not include any indication for this use.

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

April 14, 2008

Date

EXCLUSIVITY SUMMARY

NDA # 22370

SUPPL #

HFD # 170

Trade Name N/A

Generic Name tramadol hydrochloride extended-release capsules

Applicant Name Cipher Pharmaceuticals

Approval Date, If Known May 7, 2010

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.

Sponsor is seeking approval based on bioequivalence to Ultram ER, not based upon an efficacy trial.

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 20-281 Ultram IR
NDA# 21-692 Ultram ER
NDA# 21-745 Ryzolt

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

YES NO

If yes, explain:

Name of person completing form: Kathleen Davies, MS
Title: Senior Regulatory Health Project Manager
Date: May 6, 2010

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Deputy Division Director

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22370	ORIG-1	CIPHER PHARMACEUTICA LS LTD	TRAMADOL HYDROCHLORIDE

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

/s/

KATHLEEN M DAVIES
05/07/2010

SHARON H HERTZ
05/07/2010

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

NDA: 22-370 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAARP PDUFA Goal Date: 2/14/09 Stamp Date: 4/15/2008

Proprietary Name: _____

Established/Generic Name: Tramadol hydrochloride

Dosage Form: 100, 200, 300 mg 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: Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

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 checked="" type="checkbox"/>	Other	<u>0</u> yr. __ mo.	<u>1</u> yr. <u>11</u> mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" 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): 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 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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	2yr. 0 mo.	16 yr. 11 mo.	<input checked="" 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): (anticipated date: <u>1/1/2015</u>)							

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.

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 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.

Justification for partial waiver of pediatric studies:

The division agrees to waiver of pediatric studies in patients aged 0-2 years because chronic pain is not considered to occur in this population and studies would be highly impractical or impossible.

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

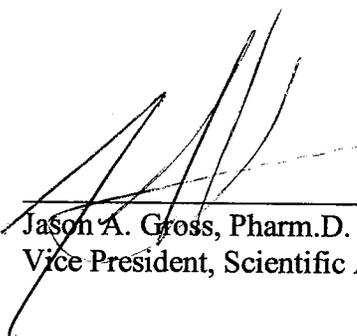
/s/

Kathleen Davies
2/11/2009 12:26:16 PM

DEBARMENT CERTIFICATION

CIP-TRAMADOL ER CAPSULES 100, 200 and 300 mg

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 in connection with this application.



Jason A. Gross, Pharm.D.
Vice President, Scientific Affairs



Date

14, 2008

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-370 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: tramadol hydrochloride extended-release capsules Dosage Form: 100, 200, 300 mg		Applicant: Cipher Pharmaceuticals Agent for Applicant (if applicable): Wilcox & Savage, P.C.
RPM: Kathleen Davies		Division: HFD-170
<p>NDA: 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>NDA 20-281 and NDA 21-692</p> <p>Provide a brief explanation of how this product is different from the listed drug. It contains both an immediate-release and extended-release component. The RLDs are each individual component. NDA 20-281 is immediate-release only and NDA 21-692 is extended-release only..</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 3/15/10</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>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>	
❖ User Fee Goal Date Action Goal Date (if different)	May 8, 2010	
❖ Actions		
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR	
• Previous actions (<i>specify type and date for each action taken</i>)	<input type="checkbox"/> None AE under NDA ^(b) ₍₄₎ , May 3, 2007, TA 2/13/ 2009	

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

❖ Advertising (*approvals only*)
Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (*indicate dates of reviews*)

- Requested in AP letter
- Received and reviewed

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <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 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 <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• If yes, exception for review granted (<i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i>)	<input type="checkbox"/> Yes
• If yes, OC clearance for approval (<i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <input type="checkbox"/>	11/17/08
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• 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

² All questions in all sections pertain 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 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 type="checkbox"/> N/A (no paragraph IV certification) <input checked="" 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>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	X
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/nonconsent 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) TA 2/13/2009
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	X
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	X
❖ Original applicant-proposed labeling	X
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	X
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 5/29/08

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	X
❖ Most recent applicant-proposed labeling	X
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 2/12/09, 4/29/10 <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If approval action, OC clearance for approval 	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ 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
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) • Incoming submissions/communications 	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings <ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) • Regulatory Briefing (<i>indicate date</i>) • Pre-NDA/BLA meeting (<i>indicate date</i>) • EOP2 meeting (<i>indicate date</i>) • Other (e.g., EOP2a, CMC pilot programs) 	<input checked="" type="checkbox"/> Not applicable <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> No mtg 9/15/05 <input type="checkbox"/> No mtg 9/24/02

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 5/29/08

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/13/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/5/09
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	12/3/08, 4/25/07, 3/15/07
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	clinical
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed 4/11/07
❖ REMS • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	11/30/06
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/18/08, 3/22/07
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 5/29/08

Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/2/08, 3/26/07
❖ DSI Clinical Pharmacology Inspection Review Summary	<input type="checkbox"/> None 9/30/08
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/16/09
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/16/09, 4/12/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/2/08, 4/16/07
• BLAs only: Facility information review(s) (<i>indicate dates</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<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	
• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs: ➤ TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)	Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

❖ NDAs: Methods Validation

- Completed
- Requested
- Not yet requested
- Not needed

Appendix A 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22370	ORIG-1	CIPHER PHARMACEUTICA LS LTD	TRAMADOL HYDROCHLORIDE

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

/s/

KATHLEEN M DAVIES
05/07/2010

From: [Davies, Kathleen](#)
To: ["Hanif Sachedina"](#);
cc: [Jason Gross](#); [Julia Chan](#);
[Stradley, Sara](#);
Subject: RE: NDA 22370 - FPI
Date: Wednesday, May 05, 2010 9:04:15 AM

Hi Hanif,

This is not acceptable. You have no tradename at this time and we do not accept placeholders for the tradename by having the established name twice. Your name for this product is tramadol hydrochloride extended-release capsules and this name is the one that should appear with prominence as you have it in color, but the exact same term below it must be deleted in terms of ease of reading and use of your product.

When you have submitted and the Agency reviews and approves a tradename, you can replace retain the display you are requesting. Until that time, the second established name must be removed from your carton and containers prior to us taking an action on this application.

Kathleen

From: Hanif Sachedina [mailto:hsachedina@cipherpharma.com]
Sent: Wednesday, May 05, 2010 7:25 AM
To: Davies, Kathleen
Cc: Jason Gross; Julia Chan; Stradley, Sara
Subject: RE: NDA 22370 - FPI

Dear Kathleen,

You are correct in that the name appears twice. The one in the colour portion is a place holder for when the brand name is determined/identified. Our understanding is that when the brand name has been accepted by FDA, we would replace "Tramadol Hydrochloride Extended Release Capsule" in the colour portion with the brand name and no other changes would be made to the label. Is that acceptable?

Regards,

hanif

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Tuesday, May 04, 2010 4:15 PM
To: Hanif Sachedina
Cc: Jason Gross; Julia Chan; Stradley, Sara
Subject: RE: NDA 22370 - FPI

Hi Hanif,

I note the carton/containers still have the name tramadol hydrochloride extended release capsules twice, once prominent in the colored portion and then again below it. As per our note below, it does not need to be on the label twice. The label should only have on it (ensuring that the established name and strength are the most prominent information on the label):

NDC Number

Tramadol hydrochloride Extended-release Capsules

dose (e.g., 100 mg)

Once daily

amount (e.g., 30 Capsules Rx only)

From: Hanif Sachedina [mailto:hsachedina@cipherpharma.com]
Sent: Tuesday, May 04, 2010 4:10 PM
To: Davies, Kathleen
Cc: Jason Gross; Julia Chan; Hanif Sachedina
Subject: NDA 22370 - FPI

Dear Kathleen,

Julia is out of the office for the next few days. Further to your request, we have made the appropriate modifications and a hard copy submission has been FedEx'd to FDA. In order to help facilitate your review, we have included in the e-mail an e-copy of the of the submission expected to be received by FDA tomorrow.

Regards,

Hanif

Hanif Sachedina B.Sc., MBA

Director, Technical Operations

Cipher Pharmaceuticals Inc.

5650 Tomken Rd. Unit 16

Mississauga, ON

Canada, L4W 4P1

T: (905) 602-5840 x346

F: (905) 602-0628

E: hsachedina@cipherpharma.com

www.cipherpharma.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]

Sent: May 3, 2010 9:38 AM

To: Julia Chan
Cc: Stradley, Sara; Jason Gross
Subject: RE: NDA 22370 - FPI

Hi Julia,

With regard to the carton/container labels, the Agency would like the statement 'extended release' instead of ER. The established name is currently on the proposed label and labeling with the term extended release, and thus it should remain as such. The term Tradename ER should be deleted only and not the established name repeated twice. Thus, your label should read, for example (ensuring that the established name and strength are the most prominent information on the label):

NDC Number

Tramadol hydrochloride Extended-release Capsules

100 mg

Once daily

30 Capsules Rx only

Warning Statement for interchanging products

From: Julia Chan [mailto:jchan@cipherpharma.com]
Sent: Friday, April 30, 2010 7:39 PM
To: Davies, Kathleen
Cc: Stradley, Sara; Jason Gross
Subject: RE: NDA 22370 - FPI

Hi Kathleen,

Thank you for the Division's comments and revisions to Cipher's package insert for NDA 22-370. Please find attached Cipher's proposed package insert in both clean

(MS Word) and tracked (PDF) formats, along with our responses to the comments provided (the Divison's comments are in bold font, and Cipher's responses are in unbolded font), and the additional proposed changes, below.

Also attached are the requested revised bottle labels for the product, with "TRADENAME ER" replaced with "TRAMADOL HCl ER CAPSULES" (it was not feasible to fit "tramadol hydrochloride extended-release capsules" in the space available, so abbreviations have been used).

1. The phrase [REDACTED] (b) (4) in the description section is promotional. We reject incorporation of this term and have removed it from the label.

Although Cipher prefers the term [REDACTED] (b) (4) we withdraw our objection to the removal of this term from the labeling.

2. The values you noted that are discrepant with Ultram ER in 14 will be updated in Ultram ER label as well. The corrected values we noted originally are values that should be included in your label and will also be included in Ultram ER's label.

Cipher acknowledges this comment.

[REDACTED] (b) (4)

(b) (4)

(b) (4)

Additional Changes to the Package Insert

In addition to the changes discussed above, Cipher has proposed the following:

- 2.1 General Dosing Considerations: Removal of cross reference (b) (4), as it is inaccurate.
- 2.8 Food Effects: Removal of the words (b) (4) as this recommendation does not apply to Cipher's product.
- Formatting and editorial changes for consistency throughout the document.

Please note that I will be out of the office next week (week of May 3, 2010), and Dr. Jason Gross, our Vice President Scientific and Medical Affairs (copied on this message), will be the contact for email correspondence in my absence. It would be appreciated, however, if you could copy me on all such correspondence. Thanks.

Kind regards,
Julia

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: April 30, 2010 1:10 PM
To: Julia Chan
Cc: Stradley, Sara
Subject: RE: NDA 22370 - FPI
Importance: High

Hi Julia,

Please find attached the Division's revisions to your PI. Note, there are extensive edits, mainly to Sections 2, 5, 7 and 12, that are intended to harmonize your PLR label to Ultram ER, your RLD, which is also being converted to PLR format. The language is not selective to your product only; it is standard language we will include in the tramadol extended release products.

Also note, the term "tradename er" is removed from your label because no trade name was submitted. Until you have an approved tradename, your label, including carton/containers, must use the established name. Please resubmit your carton and container labels with tramadol hydrochloride extended-release capsules in place of tradename er.

To address your comments submitted with the label on 4/14, please note the following:

1. The phrase (b) (4) in the description section is promotional. We reject incorporation of this term and have removed it from the label.
2. The values you noted that are discrepant with Ultram ER in 14 will be updated in Ultram ER label as well. The corrected values we noted originally are values that should be included in your label and will also be included in Ultram ER's label.

(b) (4)

Please review these changes and make any edits to the attached clean version of the label in word. Also, when responding, cc: Sara Stradley in case I am unavailable to respond to your email.

Kind Regards,

Kathleen

From: Julia Chan
Sent: April 14, 2010 11:48 AM
To: 'Davies, Kathleen'
Subject: RE: NDA 22370 - FPI

Hi Kathleen,

With reference to NDA 22-370, please find attached Cipher's response document concerning the Division's edits to our package insert, along with a tracked version of the label with our changes added to the version you sent last week. A clean version of the package insert is also provided, in case it is helpful during further review.

Kind regards,

Julia

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: April 8, 2010 2:38 PM
To: Julia Chan
Subject: NDA 22370 - FPI

Hi Julia,

Please refer to NDA 22370 for tramadol ER capsules and to your March 5, 2010 resubmission. We have reviewed the package insert and have made some edits in an effort to harmonize all the tramadol labels and edits that are specific to your product. I am attaching for your consideration. In addition, please note that this does not have final concurrence so additional edits may occur that are not included in this label.

If you could provide feedback by Wed, 4/14, I would really appreciate it.

Kind Regards,

Kathleen

From: [Davies, Kathleen](#)
To: ["Jason Gross"](#);
cc: [Stradley, Sara](#);
Subject: RE: NDA 22370 - FPI
Date: Wednesday, May 05, 2010 4:34:18 PM

Hi Jason,

Thank-you for sending this on. This label was sent in early April with this comment and, as per my email with the label, I noted that more edits may occur as upper management had not reviewed the label. In the spirit of transparency, we are working to provide comments earlier within a review cycle on labeling, which in turn can come with the downside of lack of upper level management review prior to our initial correspondence. This means that further edits may be inserted that are not reflected in the initial labeling edits. Upon further review of the label you submitted on 4/14 by Dr. Hertz, Dr. Doddapaneni, and Dr. Rappaport, (b) (4), as per our discussion today. They remain firm on this point for your label.

Please let me know how you would like to proceed once you've discussed this internally and I will be in touch with Dr. Hertz and Dr. Rappaport.

Kathleen

From: Jason Gross [mailto:jgross@cipherpharma.com]
Sent: Wednesday, May 05, 2010 3:22 PM
To: Davies, Kathleen
Subject: Fw: NDA 22370 - FPI
Importance: High

Dear Kathleen;

Per our call, we are forwarding the email, that provided insert comments.

In this correspondence the FDA specified (b) (4)
(page 2)

Based on your correspondence, it would appear that just having (b) (4)
(b) (4), would be acceptable.

Could you please advise, and we will finalize the submission with the RLD removed.

Thank you
JAG

Jason A. Gross, Pharm.D.

Vice President,
Scientific and Medical Affairs
Cipher Pharmaceuticals, INC.

5650 Tomken Road
Suite 16
Mississauga, Ontario L4W 4P1

JAG@cipherpharma.com
www.cipherpharma.com

(905) 602-5840 Ext 331

(416) 352-1853 Fax

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

From: Julia Chan

To: Jason Gross; Larry Andrews; Arshi Kizilbash, M.D.

Sent: Thu Apr 08 15:52:34 2010

Subject: FW: NDA 22370 - FPI

Hi there,

Please see the attached FDA edits to our CIP-Tramadol ER package insert, both to harmonize all tramadol labels, and to make changes re our product specifically. They are requesting feedback by April 14 (next Wed).

(b) (4)

Other requested changes:

- Under 6 ADVERSE REACTIONS, addition of cross references to relevant Warnings and Precautions subsections, and addition of subsection 6.1 Clinical Studies Experience: "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."
- Under 7 DRUG INTERACTIONS, addition of subsection 7.1 Drug Affecting Seizure Threshold: "Concomitant use of tramadol increases the seizure risk in patients taking SSRI/SNRI antidepressants or anorectics, TCA antidepressants and other tricyclic compounds, other opioids, MAOIs, neuroleptics or other drugs that lower the seizure threshold."
- Under 9 DRUG ABUSE and DEPENDENCE, addition of the following: "TRADENAME ER is an opioid with no approved use for the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia."
- Under 9 DRUG ABUSE and DEPENDENCE, addition of paragraph on withdrawal symptoms.
- Under 11 DESCRIPTION, removal of the words (b) (4), but leaving in "combination of immediate-release and extended-release components".

There were a few other more minor changes, mainly editorial. Note that the changes on the last two pages, to the Clinical Studies information which came directly from the Ultram ER label, are not reflected in the currently available Ultram ER PI online. Perhaps FDA is working on changes to the Ultram ER PI in parallel...

Please let me know your thoughts. Arshi, please could you review the safety-related changes in particular, for accuracy and comfort-level?

Thanks,
Julia

From: Davies, Kathleen [<mailto:Kathleen.Davies@fda.hhs.gov>]
Sent: April 8, 2010 2:38 PM

To: Julia Chan
Subject: NDA 22370 - FPI

Hi Julia,

Please refer to NDA 22370 for tramadol ER capsules and to your March 5, 2010 resubmission. We have reviewed the package insert and have made some edits in an effort to harmonize all the tramadol labels and edits that are specific to your product. I am attaching for your consideration. In addition, please note that this does not have final concurrence so additional edits may occur that are not included in this label.

If you could provide feedback by Wed, 4/14, I would really appreciate it.

Kind Regards,

Kathleen

From: [Davies, Kathleen](#)
To: ["Julia Chan";](#)
cc: [Stradley, Sara;](#)
Subject: RE: NDA 22370 - FPI
Date: Friday, April 30, 2010 1:09:32 PM
Attachments: [PI FDA revisions 30Apr10 clean.doc](#)
[PI FDA revisions 30Apr10.pdf](#)

Hi Julia,

Please find attached the Division's revisions to your PI. Note, there are extensive edits, mainly to Sections 2, 5, 7 and 12, that are intended to harmonize your PLR label to Ultram ER, your RLD, which is also being converted to PLR format. The language is not selective to your product only; it is standard language we will include in the tramadol extended release products.

Also note, the term "tradename er" is removed from your label because no trade name was submitted. Until you have an approved tradename, your label, including carton/containers, must use the established name. Please resubmit your carton and container labels with tramadol hydrochloride extended-release capsules in place of tradename er.

To address your comments submitted with the label on 4/14, please note the following:

1. The phrase (b) (4) in the description section is promotional. We reject incorporation of this term and have removed it from the label.
2. The values you noted that are discrepant with Ultram ER in 14 will be updated in Ultram ER label as well. The corrected values we noted originally are values that should be included in your label and will also be included in Ultram ER's label.

3.

(b) (4)

Please review these changes and make any edits to the attached clean version of the label in word. Also, when responding, cc: Sara Stradley in case I am unavailable to respond to your email.

Kind Regards,

Kathleen

From: Julia Chan
Sent: April 14, 2010 11:48 AM
To: 'Davies, Kathleen'
Subject: RE: NDA 22370 - FPI

Hi Kathleen,

With reference to NDA 22-370, please find attached Cipher's response document concerning the Division's edits to our package insert, along with a tracked version of the label with our changes added to the version you sent last week. A clean version of the package insert is also provided, in case it is helpful during further review.

Kind regards,

Julia

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]

Sent: April 8, 2010 2:38 PM
To: Julia Chan
Subject: NDA 22370 - FPI

Hi Julia,

Please refer to NDA 22370 for tramadol ER capsules and to your March 5, 2010 resubmission. We have reviewed the package insert and have made some edits in an effort to harmonize all the tramadol labels and edits that are specific to your product. I am attaching for your consideration. In addition, please note that this does not have final concurrence so additional edits may occur that are not included in this label.

If you could provide feedback by Wed, 4/14, I would really appreciate it.

Kind Regards,

Kathleen

From: [Davies, Kathleen](#)
To: ["Julia Chan";](#)
Subject: RE: NDA 22370 - FPI
Date: Thursday, April 29, 2010 1:36:55 PM

Hi Julia,

We note in your resubmission that there is no reference to your PREA requirement. The TA states that a waiver was granted for less than 2 (b) (4)

I need from you a list of dates for your PREA requirement: Protocol Submission, Study Start Date and Final Report Submission. This must be submitted officially to your NDA, but you can also provide me dates via email.

Thanks,
Kathleen

From: Julia Chan [mailto:jchan@cipherpharma.com]
Sent: Monday, April 26, 2010 2:34 PM
To: Davies, Kathleen
Subject: RE: NDA 22370 - FPI

Hi Kathleen,

Thank you for the update.

Julia

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: April 26, 2010 1:24 PM
To: Julia Chan
Subject: RE: NDA 22370 - FPI

Hi Julia,

We are currently reviewing your label with Ultram ER, your RLD, to ensure the labels are harmonized. Once we have finalized this, I will send you a

label with additional edits.

Kathleen

From: Julia Chan [mailto:jchan@cipherpharma.com]
Sent: Monday, April 26, 2010 9:21 AM
To: Davies, Kathleen
Subject: FW: NDA 22370 - FPI

Hi Kathleen,

I hope you don't mind another follow up on when we will receive some feedback, please, on our attached response to the package insert edits you provided. Any update would be appreciated.

Thanks,
Julia

From: Julia Chan
Sent: April 19, 2010 10:25 AM
To: 'Davies, Kathleen'
Subject: FW: NDA 22370 - FPI

Hi Kathleen,

I just wanted to follow up to see if you know when we can expect to receive some feedback, please, on our response to the Division's package insert edits (email below and attachments).

Many thanks,

Julia

From: Julia Chan
Sent: April 14, 2010 11:48 AM
To: 'Davies, Kathleen'
Subject: RE: NDA 22370 - FPI

Hi Kathleen,

With reference to NDA 22-370, please find attached Cipher's response document concerning the Division's edits to our package insert, along with a tracked version of the label with our changes added to the version you sent last week. A clean version of the package insert is also provided, in case it is helpful during further review.

Kind regards,

Julia

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: April 8, 2010 2:38 PM
To: Julia Chan
Subject: NDA 22370 - FPI

Hi Julia,

Please refer to NDA 22370 for tramadol ER capsules and to your March 5, 2010 resubmission. We have reviewed the package insert and have made some edits in an effort to harmonize all the tramadol labels and edits that are specific to your product. I am attaching for your consideration. In addition, please note that this does not have final concurrence so additional edits may occur that are not included in this label.

If you could provide feedback by Wed, 4/14, I would really appreciate it.

Kind Regards,

Kathleen

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22370	ORIG-1	CIPHER PHARMACEUTICA LS LTD	TRAMADOL HYDROCHLORIDE

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/s/

KATHLEEN M DAVIES
05/07/2010



NDA 022370

ACKNOWLEDGE CLASS 1 COMPLETE RESPONSE

Cipher Pharmaceuticals, Inc.
(c/o) Wilcox and Savage, P.C.
One Commercial Place, Suite 1800
Norfolk, VA 23510

Attention: Conrad M. Shumadine, Esq.
Wilcox and Savage P.C.
U.S. Agent

Dear Mr. Shumadine:

We acknowledge receipt on March 8, 2010 of your March 5, 2010 resubmission to your new drug application for tramadol hydrochloride extended-release capsules.

We consider this a complete, class 1 response to our February 13, 2009 action letter. Therefore, the user fee goal date is May 8, 2010.

If you have any questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia and Analgesia
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22370	ORIG-1	CIPHER PHARMACEUTICA LS LTD	TRAMADOL HYDROCHLORIDE

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/s/

KATHLEEN M DAVIES
03/19/2010

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

FROM:

Kathleen Davies, RPM, DAAP

DATE March 17, 2010	IND NO.	NDA NO. 022370	TYPE OF DOCUMENT Class I resubmission	DATE OF DOCUMENT March 8, 2010
NAME OF DRUG Tramadol extended-release capsules		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 23, 2010

NAME OF FIRM: Cipher Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Cipher submitted a resubmission to a tentative approval (TA) from February 13, 2009. The label was reviewed by OSE during that review cycle and an approved label was sent with the TA. The Division requests OSE re-review the approved labeling (PI and Carton/container) to ensure that the labeling still meets OSE standards. There is no proposed tradename.

This is a class I resubmission so there is a 2-month review clock. PDUFA date is May 8, 2010.

PM: Kathleen Davies

MO: Ellen Fields

Link to EDR (labeling):

<\\FDSWA150\NONECTD\N22370\S 015\2010-03-05>

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22370	ORIG-1	CIPHER PHARMACEUTICA LS LTD	TRAMADOL HYDROCHLORIDE

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/s/

KATHLEEN M DAVIES
03/17/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 12, 2009

TO: Division File

FROM: DAARP

SUBJECT: Rationale for Two NDA Numbers (NDA (b) (4) and NDA 22-370)
NDA 22-370, (Tramadol Hydrochloride Extended Release Capsules) 100, 200, 300 mg

Cipher's original NDA, (b) (4), contained an RLD to Ultram IR (NDA 20-281). This application received an AE letter on May 2, 2007. As a response to the AE letter, Cipher elected to do a PK study to demonstrate bioequivalence to Ultram IR and Ultram ER (NDA 21-692). The addition of Ultram ER as an RLD was considered a change to the application and was not permissible as a complete response. We instructed Cipher to withdraw the response and submit a new NDA. The text of our rationale is provided below.

We interpret section 505(b)(4)(A) of the Food, Drug, & Cosmetic Act (FD&C Act), added by the Medicare Modernization Act, in a manner consistent with its counterpart provision at section 505(j)(2)(D)(i), such that an applicant may not amend a 505(b)(2) application to seek approval of a drug that relies on the Agency's finding of safety and/or effectiveness for a drug that is different from the drug identified in a previous submission of the application. This interpretation also is informed by amendments to section 505(c)(3) of the FD&C Act which limit the availability of a 30-month stay of approval in certain circumstances involving amendments and supplements. Accordingly, the identification of Ultram ER as an additional listed drug relied upon is not the type of change that may be made in an amendment to a 505(b)(2) application such as a response to an approvable letter.

You may elect to withdraw and resubmit your 505(b)(2) application to identify Ultram ER as an additional listed drug relied upon. Under these circumstances, a resubmission of your application that identifies an additional listed drug relied upon and otherwise complies with section 736(a)(1)(C) of the FD&C Act would not be subject to new user fees. The Division intends to review a resubmission of this type using the same review timeframe goal that would have applied to a complete response to the approvable letter. We note that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies. Therefore, we cannot consider

6
this complete response to our action letter. The review clock will not start until we receive a complete response or a new NDA submission. If you decide to resubmit your application as a new NDA, the review clock would be the equivalent of a Class 2 resubmission and would have a six-month review clock.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22370	ORIG-1	CIPHER PHARMACEUTICA LS LTD	TRAMADOL HYDROCHLORIDE

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/s/

SARA E STRADLEY

05/10/2010

Internal memo to link the NDA 22370 and (b) (4)

From: [Davies, Kathleen](#)
To: ["Julia Chan"](#);
Subject: NDA 22370 follow up regarding teleconference
Date: Friday, November 07, 2008 11:08:01 AM

Hi Julia,

Please refer to NDA 22370 for tramadol ER capsules. I spoke with our PREA group regarding your questions at the teleconference.

(b) (4)



I hope this is helpful for you.

Kathleen

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22370	ORIG-1	CIPHER PHARMACEUTICA LS LTD	TRAMADOL HYDROCHLORIDE

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/s/

KATHLEEN M DAVIES
02/03/2010

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/s/

Kathleen Davies
7/23/2008 05:20:53 PM

MEMORANDUM OF TELECON

DATE: May 29, 2008

APPLICATION NUMBER: NDA 22-370

BETWEEN:

Name: Cipher Pharmaceuticals
Phone: 1-866-368-6248

AND

Name: Sharon Hertz, MD, Deputy Division Director, DAARP
Mwango Kashoki, MD, Clinical Team Leader, DAARP
Suresh Doddapaneni, PhD, Clinical Pharmacology Team Leader, OCP
Lei K. Zhang, PhD, Clinical Pharmacology Reviewer, OCP
DAARP, HFD-170

SUBJECT: Requested additional pharmacokinetic (PK) data for new NDA 22-370

FDA sent an information request (IR) to Cipher on May 17, requesting additional information to support their NDA. The request is as stated:

(b) (4) you have elected to support your NDA with reliance upon the Agency's previous determination of safety and efficacy of Ultram ER (N 21-692), and demonstration of bioequivalence of your product to Ultram ER tablets. However, data from the two new submitted pharmacokinetic studies (TRAMPK.07.01 and TRAMPK.07.04) assessed bioequivalence only between the 300 mg strengths of your product and Ultram ER Tablets. Data demonstrating a similar link between the 200 mg and 100 mg strengths of your product and Ultram ER Tablets were not submitted. This information is necessary, given your current regulatory approach towards NDA approval. Provide bioequivalence data comparing the 100 mg and 200 mg strengths of your product and Ultram ER Tablets, and/or a scientific rationale demonstrating the link between the 200 mg and 100 mg strengths of the two products.

Cipher responded on May 22, stating that all data was provided in the application and no new additional information was required.

The Division requested a teleconference with Cipher after receiving the May 22 submission so that we could thoroughly explain what was deficient in their application. Dr. Doddapaneni explained that the data on their product already included in the application: bioequivalence under fasted and fed, dose proportionality and dissolution data, are supportive and will be reviewed. However, Dr. Doddapaneni explained that what is missing from this application is the link between Cipher's product and the approved marketed reference listed drug (RLD), Ultram

ER, for the 100- and 200-mg strengths. He further explained that the the comparative dissolution data to compare CIPHER's tramadol product to the RLD in three media pHs, as described in the Guidance ("Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations") can be used to support the missing link for the 100 and 200 mg strengths. f_2 values of ≥ 50 would suggest similar dissolution profiles and no further *in vivo* BE studies between the CIPHER's tramadol product and the RLD are needed.

CIPHER inquired as to the criticality of this data. The Division explained that, if CIPHER intends to rely upon the safety and efficacy of Ultram ER as a basis for approval of their product, then this data is required to make a determination on approval for their product. The Division further stated that they would like the data prior to the filing date of June 13.

CIPHER explained that they would not be able to provide this data by June 13. The Division agreed to make a specific exception for this situation only and agreed that CIPHER could have until the end of June to produce this data and submit it to the NDA, even though it was past the filing date. The Division also cautioned CIPHER that, if the dissolution data turns out to be inadequate to support approval, then *in vivo* data will be required. The Division explained that this was a risk CIPHER was taking in agreeing to submit this data during the review. CIPHER acknowledged this advice and stated they would submit a letter to the NDA agreeing to submit the requested dissolution data by June 30.

Kathleen Davies
Regulatory Health Project Manager

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/s/

Kathleen Davies
6/27/2008 12:21:39 PM
CSO



FILING COMMUNICATION

NDA 22-370

Cipher Pharmaceuticals Inc.
(c/o) Willcox & Savage, P.C.
One Commercial Place, Suite 1800
Norfolk, VA 23510

Attention: Conrad M. Shumadine, Esq.
U.S. Agent

Dear Mr. Shumadine:

Please refer to your new drug application (NDA) dated April 14, 2008, received April 15, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for tramadol hydrochloride 100, 200, 300 mg.

We also refer to your submissions dated May 22 and June 4, 2008.

We also refer to the teleconference held between you and the Division on May 29, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. During the May 29, 2008 teleconference, you committed to provide the dissolution data for the 100- and 200-mg strengths of your product by June 30, 2008. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is February 15, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We note that you have not fulfilled the requirement.

(b) (4)

If you have any questions, call Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
6/13/2008 07:19:44 PM

From: [Davies, Kathleen](#)
To: ["Julia Chan";](#)
CC:
Subject: NDA 22370 - Request for Information
Date: Thursday, June 12, 2008 11:36:33 AM
Attachments: [Blank Bkgrd.gif](#)

Hi Julia,

Please refer to NDA 22-370 for cip-tramadol. We have the following information request regarding this application:

You have provided a proposed label that contains the adverse reaction experience for Ultram ER. You will need to revise the label to include the clinical trial adverse reaction experience for your product. Submit an updated integrated safety dataset and the new label for our review by June 30, 2008.

If you have any questions, please let me know.

Kathleen

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/s/

Kathleen Davies
6/12/2008 01:43:53 PM
CSO

From: [Davies, Kathleen](#)
To: ["Julia Chan";](#)
CC:
Subject: NDA 22-370 Trade Name
Date: Wednesday, May 07, 2008 11:03:41 AM
Attachments: [Blank Bkgrd.gif](#)

Hi Julia,

Please refer to NDA 22-370 and to NDA (b) (4) for Cip-tramadol. The trade names "(b) (4)" and "(b) (4)" were submitted to NDA (b) (4) for review by DDMAC and by OSE. These names are also proposed under NDA 22-370.

OSE does not recommend the use the proprietary names "(b) (4)" and "(b) (4)". "(b) (4)" can look similar to Trimplex, Luvox, and Vermox when scripted. "(b) (4)" can look similar to Tiazac and Tasmар when scripted. Please propose alternative tradenames for this pending product that will minimize potential user error.

In addition, because this is an extended release product, it must be clearly identified in the established name. The labeling must reflect "extended release" in conjunction with the established name, tramadol. For example: (tramadol hydrochloride) extended-release capsules.

If you have any questions, let me know.

Kind Regards,

Kathleen Davies, MS
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of New Drugs
Center for Drug Evaluation and Research

Phone: (301) 796-2205

Email: kathleen.davies@fda.hhs.gov

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/s/

Kathleen Davies
5/7/2008 11:05:41 AM
CSO



NDA 22-370

NDA ACKNOWLEDGMENT

Cipher Pharmaceuticals Inc.
(c/o) Willcox & Savage, P.C.
One Commercial Place, Suite 1800
Norfolk, VA 23510

Attention: Conrad M. Shumadine, Esq.
U.S. Agent

Dear Mr. Shumadine:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tramadol Hydrochloride 100, 200, 300 mg

Date of Application: April 14, 2008

Date of Receipt: April 15, 2008

Our Reference Number: NDA 22-370

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 June 14, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

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

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

If you have any questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, MS
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kathleen Davies
4/16/2008 01:52:14 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND (b) (4)

Cipher Pharmaceuticals, Ltd.
c/o Galephar PR, Inc.
Road 198 No. 100 km 14.7
Juncos Industrial Park
Juncos, PR 00777-3873

Attention: Arthur M. Deboeck
Vice President and Global Manager (U.S. Agent)

Dear Mr. Deboeck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tramadol ER, 100, 200 and 300 mg Capsule.

We also refer to your September 14, 2005 correspondence, received September 15, 2005, requesting a pre-NDA meeting to discuss and gain agreement on the overall content and presentation of data in planned NDA submission for CIP-TRAMADOL ER 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.

If you have any questions, call me at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Paul Z. Balcer
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 21, 2005

TIME: 2:00-3:00 p.m. (EST)

LOCATION: FDA (White Oak), Conference Rm#1417, 10903 New Hampshire Ave, Silver Spring, MD 20993

APPLICATION (DRUG): IND (b) (4) Tramadol ER, 300 mg Capsule

INDICATION: Management of moderate to moderately severe chronic pain.

SPONSOR: Cipher Pharmaceuticals, Ltd. (b) (4)

TYPE OF MEETING: Type B, Pre-NDA

MEETING CHAIR: Bob A. Rappaport, M.D.

MEETING RECORDER: Paul Z. Balcer, RPM

MEETING OBJECTIVE: Sponsor requested discussion and gain agreement on the overall content and presentation of data in planned NDA submission for CIP-TRAMADOL ER Capsules

BACKGROUND:

Meeting request: September 14, 2005, received September 15, 2005

Meeting package: October 24, 2005, received October 25, 2005

A type B meeting was granted on October 5, 2005.

FDA Attendees

Name	Title
Curtis Rosebraugh, M.D.	Deputy Director, Office of Drug Evaluation II
Bob Rappaport, M.D.	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Sharon Hertz, M.D.	Deputy Director (Pain Team)
Mwango Kashogi, M.D.	Clinical Team Leader (Pain Team)
Joel Schiffenbauer, M.D.	Clinical Team Leader (Rheumatology Team)
Julia Castle, M.D., M.P.H.	Assigned Clinical Reviewer
Thomas J. Permutt, Ph.D.	Statistics Team Leader
Katherine B. Meaker, M.S.	Statistics Reviewer
David J. Lee, Ph.D.	Clinical Pharmacology Reviewer
Dan Mellon, Ph.D.	Pharmacology/Toxicology Team Leader
Asoke Mukherjee, Ph.D.	Pharmacology/Toxicology Reviewer
Paul Z. Balcer	Regulatory Project Manager

Cipher Pharmaceuticals, Ltd. Attendees

Name	Title
Larry Andrews	President, Cipher Pharmaceuticals, Ltd.
(b) (4)	
(b) (4)	
Arthur Deboeck	VP & General Manager, Galephar PR, Inc. (U.S. Agent for Cipher)
Janet McDougall, M.D	Cipher Pharmaceuticals Ltd. (via teleconference)

QUESTIONS from SPONSOR and FDA COMMENTS:

Clinical

- Cipher believes that they have completed all of the analyses that the Agency considers necessary. Does the Agency agree?*

FDA response:

Yes.

Discussion

(b) (4)

(b) (4)

FDA Response:

(b) (4)

Discussion

(b) (4)

Integrated Safety Database

3. *Sample Tables and Listings for the integrated safety database, that will form the basis for the safety summary for the CTD are provided in Appendix 2. The same format will be used for the 120 day safety update. Cipher requests the Agency's comments on the proposed tables and listings. In particular:*
 - i. *Are the tables and listings acceptable to the Agency and are there any additional tables and listings that the Agency would like to see?; and*
 - ii. *Is the format acceptable for the Agency? Please note that although data have been included in the tables, these are not final data, but have been included only to aid in decisions regarding format.*

FDA Response:

The tables and listings and format appear acceptable. We are unclear about the absence of deaths in the safety tables or listings, please clarify.

Please provide an integrated safety dataset that includes safety data from all of the clinical trials. This dataset should be a SAS transport file and include unique patient identifiers, coded terms, verbatim terms, dose assignment, and duration of event or start and stop dates.

Discussion

Cipher reported one death in their studies, however it is unknown whether it occurred in the active drug or placebo arm due to blinding of the study. Cipher was asked to include patient demographics in the integrated safety dataset.

Alcohol Interaction

4. *Is there enough data from the in vitro data to satisfy the Agency's concerns?*

FDA Response:

To be discussed.

Discussion

This Tramadol ER formulation behaves like an IR formulation when subjected to alcohol in vitro. The Division was unable to find any existing clinical safety information on a 300-mg Tramadol IR dose. Additionally, the Division expressed concern regarding overdose resulting in seizures. Since the Division has safety concerns, the interaction of Tramadol and EtOH needs to be investigated prior to filing of the NDA. Therefore, Cipher needs to perform an interaction study between a 300-mg Tramadol IR dose and EtOH. The Division asked Cipher to provide a protocol for the study design, employing a population of heavy drinkers in order to show in vivo results.

Biopharmaceutics

5. *The biopharmaceutics package has been previously reviewed with the Agency (September 24, 2002 meeting).* (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

Discussion

There was no additional discussion beyond the information provided in the slide.

Nonclinical

6. *Cipher has previously indicated that no new nonclinical data will be provided with the NDA, and the Agency's previous findings for Tramadol will also be relied upon. A summary and discussion of relevant published literature will be provided. Is this acceptable to the Agency?*

FDA Response:

Yes. The proposed label should be updated to conform to 21 CFR § 201.57.

We recommend that you consult the Draft Guidance on 505(b)(2) applications during preparation of your NDA. Several key concepts from that guidance are highlighted in the following information.

- The following reference is available on the CDER website: October 1999 DRAFT Guidance for Industry: Applications Covered by Section 505(b)(2)
- For a 505(b)(2) application you must include the following:
 - Clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference.
- A 505(b)(2) application that relies upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.

- A 505(b)(2) application relying upon literature must clearly identify the listed drug(s) on which the studies were conducted (if any).
- For a 505(b)(2) application you must provide a patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). -- (Listed in the Orange Book)
 - Patent certification should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.
 - You must also submit a relative bioavailability study comparing the proposed product to the listed drug(s) (if any).

Key Issue regarding the requirement for appropriate patent certification: Due to legislation contained in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), if during the review of an NDA filed under 505(b)(2), either the applicant decides to refer to a different product than that/those identified in the original application, or the Agency discovers that the applicant did not appropriately certify to the patent(s) of the products referenced in the original application, then the applicant would be required to withdraw and resubmit the application as a new original NDA, with the appropriate Patent Certifications included, potentially requiring a new User Fee.

- Before submitting your NDA, the guidance recommends that you submit a plan to the reviewing Division that specifically identifies the types of bridging studies that will be conducted. You should also identify those components of its application for which you expect to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The Division will critique the plan and provide guidance.
- The review of this plan will be completed around Division deadlines that may take higher priority; therefore, the Division encourages that you submit such a plan well in advance of the NDA submission, to provide adequate time for the reviewer to evaluate the proposal and resolve any potential concerns that may result in a filing issue or delay in the review process.
- If the only literature that you submit is within the public domain and/or you have right of reference to the studies and the data required to support them, you may be able to submit a 505(b)(1) application.
- If portions of your application rely upon studies that you do not have right of reference to or are not within the public domain, you must submit a 505(b)(2) application. Please note that not all studies reported in the literature are supported by data that exists within the public domain. Many studies in the literature are supported by proprietary data.

Discussion

[REDACTED] (b) (4)

Administrative Information & Format

7. [REDACTED] (b) (4)

[REDACTED]

Discussion

There was no additional discussion beyond the information provided in the slide.

8. *A description of the overall format and presentation of the submission is provided in Appendix 5. Does the Agency consider the proposed format/presentation of data satisfactory?*

FDA Response:

The description of overall format and presentation of the NDA is acceptable. We encourage you to refer to the *Guidance for Industry, M4: Organization of the CTD (8/2001)* and the latest *Guidance for Industry, Granularity Document, Annex to M4: Organization of the CTD (10/2005)*. You may also consider submitting your NDA in the eCDT format; for more information access CDER's Electronic Common Technical Document web site at <http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

Discussion

There was no additional discussion beyond the information provided in the slide.

Action Items

1. **The Division and CIPHER agreed to further discuss the regulatory aspects of the NDA application in a separate meeting.**
2. [REDACTED] (b) (4)
3. **CIPHER was asked to include patient demographics in the integrated safety dataset.**
4. **CIPHER was asked to perform a clinical interaction study between a 300-mg Tramadol IR and EtOH, and to provide a protocol for the study design, employing a population of heavy drinkers in order to show in vivo results.**

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/s/

Paul Balcer
12/20/2005 01:56:05 PM



(b) (4)

Cipher Pharmaceuticals, Ltd.
c/o Galephar PR, Inc.
Attention: Arthur M. Deboeck
Vice President and Global Manager (U.S. Agent)
Road 198 No. 100 km 14.7
Juncos Industrial Park
Juncos, PR 00777-3873

Dear Mr. DeBoeck:

Please refer to the End of Phase II IND (type A) meeting between representatives of your firm and FDA on April 26, 2005. The purpose of the meeting was to discuss the clinical development plan for Tramadol ER, and verify Cipher's existing clinical development plan, following the April 22, 2005 Regulatory Briefing

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 Paul Z. Balcer, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page.}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

MEETING DATE: April 26, 2005

TIME: 1:00-2:00 p.m.

LOCATION: S300, 9201 Corporate Boulevard, Rockville, MD

APPLICATION (DRUG): IND (b) (4) Tramadol ER

SPONSOR: Cipher Pharmaceuticals, Ltd., Mississauga, ON Canada

TYPE OF MEETING: Type A, face to face

MEETING CHAIR: Sharon Hertz, M.D.

MEETING RECORDER: Paul Z. Balcer

MEETING OBJECTIVE: Cipher Pharmaceuticals, Ltd. requests FDA review the clinical development plan for Tramadol ER, and verify Cipher's existing clinical development plan, following the April 22, 2005 Regulatory Briefing.

BACKGROUND:

Meeting request: February 3, 2005, received February 4, 2005

Meeting package: March 30, 2005, received March 31, 2005

On January 31, 2005, Cipher Pharmaceuticals, Ltd and FDA held a meeting to discuss both the TRAMCT.02.05 protocol and the entire clinical development plan for the Tramadol ER. On February 3, 2005 Cipher requested another Type A meeting to take place after the FDA Regulatory Briefing on Tramadol, which was held on April 22, 2005.

FDA Attendees

Name of FDA Attendee	Title
Brian E. Harvey, MD, PhD	Deputy Director ODEV Acting Director, HFD-550
Sharon Hertz, MD	Deputy Director
James Witter, MD, PhD	Assigned Clinical Team Leader
Joel Schiffenbauer, MD	Clinical Team Leader
Julia Castle, MD	Clinical Reviewer
Atiar Rahman, PhD	Statistics Reviewer
Dennis Bashaw, PharmD	Clinical Pharmacology & Biopharmaceutics Team Leader
Carmen DeBellas, RPh	Chief Project Manager

Paul Z. Balcer	Regulatory Project Manager
----------------	----------------------------

External Constituent Attendees

External Attendee	Title
Larry Andrews	President, Cipher Pharmaceuticals, Ltd.
(b) (4)	
Arthur Deboeck	VP & General Manager, Galephar PR Inc. (US Agent for Cipher)

(b) (4)

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/s/

Sharon Hertz
5/17/05 01:04:27 PM
Signing for Bob Rappaport, M.D.



(b) (4)

Cipher Pharmaceuticals, Ltd.
c/o Galephar PR, Inc.
Attention: Arthur DeBoeck
Juncos Industrial Park
Juncos, PR 00777-32

Dear Mr. DeBoeck:

Please refer to the End of Phase II IND teleconference meeting between representatives of your firm and FDA on December 31, 2004. The purpose of the meeting was to discuss the TRAMCT.02.05 protocol and (b) (4) protocols TRAMCT.02.02 and TRAMCT.02.4 in light of December 8, 2004 and January 28, 2005 letters from FDA.

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 Paul Z. Balcer, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page.}

Sharon Hertz, M.D.
Deputy Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure



TELECONFERENCE MEETING MINUTES

MEETING: End of Phase 2 (type B)
DATE, TIME: January 31, 2005, 3:00 p.m. – 4:00 p.m. (EST)
LOCATION: CDER CORP2 S300 Conf. Room
APPLICATION: IND (b) (4)
DRUG: Tramadol[®] ER, 300 mg Capsule
INDICATION: Relief of signs and symptoms of osteoarthritis of the hip and knee.
SPONSOR: Cipher Pharmaceuticals, Ltd.

OBJECTIVE:

The purpose of the meeting was to discuss the TRAMCT.02.05 protocol and (b) (4) protocols TRAMCT.02.02 and TRAMCT.02.4 in light of December 8, 2004 and January 28, 2005 letters from FDA. The sponsor also wanted to gain FDA agreement that this protocol will serve to complete the Tramadol ER clinical development plan.

BACKGROUND:

- Submission from sponsor: N-0023, dated October 5, 2004 and received October 7, 2004.
- FDA letters to Sponsor: December 8, 2004 and January 28, 2005.
- Meeting Request: N-0024, dated December 20, 2004 and received December 22, 2004.
- Meeting Package: N-0025, dated January 14, 2005 and received January 19, 2005.

FOOD AND DRUG ADMINISTRATION (FDA) PARTICIPANTS:

Center for Drug Evaluation and Research (CDER),

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP)

- Sharon Hertz, M.D. – Deputy Director, DAAODP
- Joel Schiffenbauer, M.D. – Medical Team Leader
- James P. Witter, M.D., Ph.D. – Medical Team Leader
- M. Atiar Rahman, Ph.D. – Biostatistics Reviewer
- Carmen DeBellis, R.Ph. – Chief, Project Management Staff
- Paul Z. Balcer – Regulatory Health Project Manager

SPONSOR PARTICIPANTS:

Cipher Pharmaceuticals, Ltd.

- Larry Andrews – President
- Arthur DeBoeck – U.S. Agent for Cipher, Galephar PR, Inc. (via teleconference)

Consultants

- (b) (4)

(b) (4)

(b) (4)

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/s/

Sharon Hertz
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(b) (4)

Cipher Pharmaceuticals, Ltd.
c/o Galephar PR, Inc.
Attention: Arthur DeBoeck
Juncos Industrial Park
Juncos, PR 00777-32

Dear Mr. DeBoeck:

Please refer to the End of Phase II IND Meeting between representatives of your firm and FDA on July 16, 2004. The purpose of the meeting was to discuss FDA's guidance on the interpretation of the study results to date, (b) (4) and discuss an interim analysis of a 12 week data from the ongoing safety study 02.04.

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 Paul Z. Balcer, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page.}

Sharon Hertz, M.D.
Deputy Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure



MEETING MINUTES

MEETING: End of Phase 2 (type B)
DATE, TIME: July 16, 2004, 11:09 a.m. –11:58 a.m. (EST)
LOCATION: CDER CORP2 S300 Conf. Room
APPLICATION: IND (b) (4)
DRUG: Tramadol[®] ER, 300 mg Capsule
INDICATION: Relief of signs and symptoms of osteoarthritis of the hip and knee.
SPONSOR: Cipher Pharmaceuticals, Ltd.

OBJECTIVE:

The purpose of the meeting was to discuss FDA's guidance on the interpretation of the study results to date, (b) (4) and to discuss an interim analysis of a 12 week data from the ongoing safety study 02.04.

BACKGROUND:

- Meeting Request: N-0018, dated May 25, 2004 and received May 26, 2004.
- Meeting Packages: N-0019, dated June 14, 2004 and received June 15, 2004 and N-0020, dated June 29, 2004 and received July 1, 2004..

FOOD AND DRUG ADMINISTRATION (FDA) PARTICIPANTS:

Center for Drug Evaluation and Research (CDER),

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP)

- Brian E. Harvey, M.D., Ph.D. – Acting Director DAAODP/Deputy Director ODE V
- Terri Rumble, – Associate Director of Regulatory Affairs, ODE V
- Sharon Hertz, M.D. – Deputy Director, DAAODP
- Joel Schiffenbauer, M.D. – Medical Team Leader
- James P. Witter, M.D., Ph.D. – Medical Team Leader
- Lourdes Villalba, M.D. – Medical Reviewer
- Carolyn L. Yancey, M.D. – Medical Reviewer
- M. Atiar Rahman, Ph.D. – Biostatistics Reviewer
- Meyer Katzper, Ph.D. – Operations Research Analyst
- Carmen DeBellis, R.Ph. – Chief, Project Management Staff
- Paul Z. Balcer – Regulatory Health Project Manager

SPONSOR PARTICIPANTS:

Cipher Pharmaceuticals, Ltd.

- Larry Andrews – President
- Arthur DeBoeck – U.S. Agent for Cipher, Galephar PR, Inc. (via teleconference)

Consultants

(b) (4)

■ [REDACTED] (b) (4)

DISCUSSION:

After opening remarks and introductions, the participants of this meeting discussed the questions below, included in the Meeting Package dated June 14 and 29, 2004, sent by Mr. Andrews.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

3. Finally, Cipher is currently conducting a long term safety study of Tramadol ER numbered 02.04 and entitled: "A double-blind, placebo-controlled, phase III safety study of Tramadol ER 300 mg taken once-daily for the relief of signs and symptoms of osteoarthritis of the hip and knee". Patients are to be titrated at one week intervals from 100 mg OD to 300 mg OD and then remain at this dose for a period of twelve months.

Additional comments:

The Agency considered this to be a guidance meeting.

The Division requests that when resubmitting a revised protocol, the Sponsor include reference to the past protocols so that the reviewing staff can look at the totality of the information.

ACTION ITEMS:

- The Division will provide a copy of the minutes.

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/s/

Sharon Hertz
8/5/04 11:39:36 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 24, 2002

TIME: 10:00 EDT

LOCATION: S300

APPLICATION: IND (b) (4) (Cipher Oral Tramadol ER Capsules)

TYPE OF MEETING: End of Phase II ,Type B meeting

MEETING CHAIR: Dr. Lourdes Villalba

MEETING RECORDER: Nancy M.Halonen, Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division / Name/ HFD#</u>
Jonca Bull, M.D.	Office Director	ODE V
Lawrence Goldkind, M.D.	Deputy Director	FDA/DAAOOP/HFD-550
James Witter, M.D.,Ph.D.	Medical Team Leader	FDA/DAAOOP/HFD-550
Lourdes Villalba, M.D.	Medical Reviewer	FDA/DAAOOP/HFD-550
John Smith, PhD.	Chemistry Team Leader	FDA/DAAOOP/HFD-550
Joel Schiffenbauer, M.D.	Medical Reviewer	FDA/DAAOOP/HFD-550
Tatiana Oussava, M.D.	Medical Reviewer	FDA/DAAOOP/HFD-550
Stan Lin, Ph.D.	Statistical Team Leader	FDA/DAAOOP/HFD-550
Suktae Choi, PhD.	Statistical Reviewer	FDA/DAAOOP/HFD-550
Dennis Bashaw, PharmD	Biopharmacology Team Leader	FDA/DAAOOP/HFD-550
Carmen Debellas, R.Ph.	Chief Project Manager	FDA/DAAOOP/HFD-550
Nancy Halonen, BSN,CDE	Project Manager	FDA/DAAOOP/HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
Ian W. French, PhD.	President	Cipher Canada Inc.
Larry S. Gontovnick, PhD.	Vice-President, Clinical Development Regulatory Affairs	Cipher Canada Inc.
Arthur deBoeck	U.S. Agent	Galephar Pharm., Inc.

(b) (4)

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Minutes Preparer: Nancy Halonen, CSO

Chair Concurrence: Dr. Lourdes Villalba

cc: Original

HFD-550/Div. Files

HFD-550/Meeting Minutes files

HFD-550/RPM

HFD-550/Reviewers & Attendees

Drafted by nh 6-4-02

Initialed by: JW

final: 10-1-02

MEETING MINUTES

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/s/

Lee Simon

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