

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022450Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PATENT CERTIFICATION UNDER 21 CFR 314.50(i)

In the opinion and to the knowledge of Cadence Pharmaceuticals, Inc., there are no patents, other than patents to which Cadence Pharmaceuticals, Inc., has a right of reference, which claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.



Hazel M. Aker
SVP & General Counsel
Cadence Pharmaceuticals, Inc.

April 24, 2009
Date

PATENT CERTIFICATIONS

Cadence Pharmaceuticals, Inc. hereby certifies that the provisions of 21 U.S.C 355(b)(2) or (j)(2)(A) do not apply to this application.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-450

NAME OF APPLICANT / NDA HOLDER

Cadence 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)

ACETA VANCE

ACTIVE INGREDIENT(S)

Acetaminophen

STRENGTH(S)

1 g per 100 mL

DOSAGE FORM

Injection Solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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

FDA will not list patent information if you 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

6,028,222

b. Issue Date of Patent

February 22, 2000

c. Expiration Date of Patent

August 5, 2017

d. Name of Patent Owner

SCR Pharmatop

Address (of Patent Owner)

Residence Concorde - 10, SQUARE SAINT-FLORENTINE

City/State

LE CHESNAY, FRANCE

ZIP Code

78150

FAX Number (if available)

0030(1)39556105

Telephone Number

0030(1)39545577

E-Mail Address (if available)

scr.pharmatop@gmail.com

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)

 Charles A. Muserlian

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

HEDMAN & COSTIGAN, P.C.

1185 Avenue of the Americas

City/State

New York, NY

ZIP Code

10036-2646

FAX Number (if available)

212.302.8998

Telephone Number

212.302.8989

E-Mail Address (if available)

mail@hgcpatent.com

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

Yes

No

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

Yes

No

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 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.)

5. No Relevant Patents

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

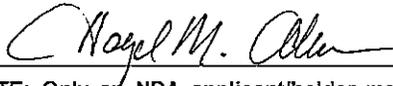
6. Declaration Certification

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

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

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

Date Signed



April 30, 2009

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

Hazel M. Aker for Cadence Pharmaceuticals, Inc.

Address

12481 High Bluff Drive, Suite 200

City/State

San Diego, CA

ZIP Code

92130

Telephone Number

(858) 436-1400

FAX Number (if available)

(858) 436-8510

E-Mail Address (if available)

haker@cadencepharm.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.

**PATENT INFORMATION SUBMITTED WITH THE
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ACETA VANCE

ACTIVE INGREDIENT(S)

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Injection Solution

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1. GENERAL

a. United States Patent Number

6,992,218

b. Issue Date of Patent

January 31, 2006

c. Expiration Date of Patent

June 6, 2021

d. Name of Patent Owner

SCR Pharmatop

Address (of Patent Owner)

Residence Concorde - 10, SQUARE SAINT-FLORENTINE

City/State

LE CHESNAY, FRANCE

ZIP Code

78150

FAX Number (if available)

0030(1)39556105

Telephone Number

0030(1)39545577

E-Mail Address (if available)

scr.pharmatop@gmail.com

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)

Charles A. Muserlian

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

HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas

City/State

New York, NY

ZIP Code

10036-2646

FAX Number (if available)

212.302.8998

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212.302.8989

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mail@hgcpatent.com

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

Yes

No

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- 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
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- 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
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- 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

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- 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.)

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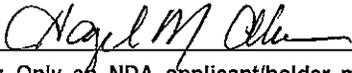
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Date Signed



April 30, 2009

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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

Hazel M. Aker for Cadence Pharmaceuticals, Inc.

Address

12481 High Bluff Drive, Suite 200

City/State

San Diego, CA

ZIP Code

92130

Telephone Number

(858) 436-1400

FAX Number (if available)

(858) 436-8510

E-Mail Address (if available)

haker@cadencepharm.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.

EXCLUSIVITY SUMMARY

NDA # 022450

SUPPL #

HFD # 170

Trade Name Ofirmev

Generic Name Acetaminophen Injection

Applicant Name Cadence Pharmaceuticals

Approval Date, If Known November 2, 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.

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?

3 years

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# 21123 (Ultracet) and
others

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical

investigations submitted in the application that are essential to the approval:

CPI-APF-302, RC 210 3 002 and CPI-APA-304

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

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

YES

NO

If yes, explain:

=====

Name of person completing form: Parinda Jani

Title: Chief, Project Management Staff

Date:

Name of Office/Division Director signing form: Sharon Hertz, M.D.

Title: Deputy Director, DAAP

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

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

/s/

PARINDA JANI
11/02/2010

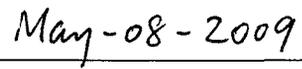
SHARON H HERTZ
11/02/2010

CERTIFICATE OF DEBARMENT

Cadence 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.



Malcolm Lloyd-Smith
Senior VP, Regulatory Affairs and Quality Assurance
Cadence Pharmaceuticals, Inc.



Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

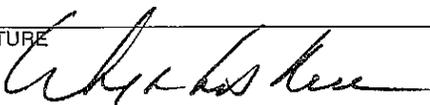
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the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

Please mark the applicable checkbox.

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

Clinical Investigators	Please see attached list of clinical investigators	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME William R. LaRue	TITLE SVP, CFO, Treasurer and Assistant Secretary
FIRM/ORGANIZATION Cadence Pharmaceuticals, Inc.	
SIGNATURE 	DATE 4/30/09

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

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

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

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

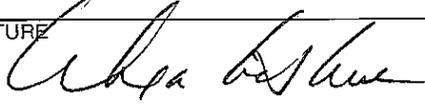
Please mark the applicable checkbox.

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

Clinical Investigators		

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

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

NAME William R. LaRue	TITLE SVP, CFO, Treasurer and Assistant Secretary
FIRM/ORGANIZATION Cadence Pharmaceuticals, Inc.	
SIGNATURE 	DATE 4/30/09

Paperwork Reduction Act Statement

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Department of Health and Human Services
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5600 Fishers Lane, Room 14C-03
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CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

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

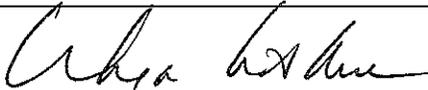
Please mark the applicable checkbox.

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

Clinical Investigators		

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

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

NAME William R. LaRue	TITLE SVP, CFO, Treasurer and Assistant Secretary
FIRM/ORGANIZATION Cadence Pharmaceuticals, Inc.	
SIGNATURE 	DATE 4/30/09

Paperwork Reduction Act Statement

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

Stradley, Sara

From: Stradley, Sara
Sent: Friday, October 29, 2010 3:35 PM
To: 'Malcolm Lloyd-Smith'
Cc: Jani, Parinda; Stradley, Sara
Subject: Labeling

Hi Malcolm

Drs Rappaport, Hertz, and Rosebraugh have discussed the labeling and agree on the following.

14.1 Adult Acute Pain

The efficacy of OFIRMEV in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain.

Pain Study 1 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg vs. placebo every 6 hours for 24 hours in 101 patients with moderate to severe pain following total hip or knee replacement. OFIRMEV was statistically superior to placebo for reduction in pain intensity over 24 hours. There was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

Please revise the label and send us an electronic version by email as soon as possible.
Thanks

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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/s/

SARA E STRADLEY
11/01/2010

Stradley, Sara

From: Stradley, Sara
Sent: Tuesday, October 26, 2010 9:08 AM
To: 'Malcolm Lloyd-Smith'
Cc: Jani, Parinda; Stradley, Sara
Subject: NDA 022450 comments on Revised Label

Hi Malcolm

We note the one following point in the PI that is unsettled:

14.1 Adult Acute Pain

The efficacy of OFIRMEV in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain.

Pain Study 1 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg vs. placebo every 6 hours for 24 hours in 101 patients with moderate to severe pain following total hip or knee replacement. OFIRMEV was statistically superior to placebo for reduction in pain intensity over 24 hours. There was an attendant decrease in (b) (4) opioid consumption (b) (4), the clinical benefit of which was not demonstrated.

We have discussed this internally extensively, and, in the absence of an identified clinical benefit to the lower consumption of opioid, the proposed language is unacceptable and should be changed back to the following:

14.1 Adult Acute Pain

The efficacy of OFIRMEV in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain.

Pain Study 1 evaluated the analgesic efficacy of repeated doses of OFIRMEV 1000 mg vs. placebo every 6 hours for 24 hours in 101 patients with moderate to severe pain following total hip or knee replacement. OFIRMEV was statistically superior to placebo for reduction in pain intensity (b) (4)

Please provide your response by COB today. Thanks.

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

10/27/2010

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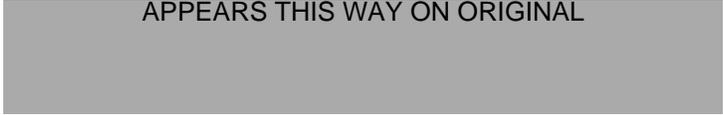
/s/

SARA E STRADLEY
10/27/2010

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

APPEARS THIS WAY ON ORIGINAL



Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

ORIG-1

CADENCE
PHARMACEUTICA
LS INC

Ofirmev (acetaminophen for
injection)

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/s/

PARINDA JANI
05/20/2010



NDA 022450

ACKNOWLEDGE CLASS 2 RESPONSE

Cadence Pharmaceuticals, Inc.
12481 High Bluff Drive Suite # 200
San Diego, CA 92130

Attention: Tracy Ross-Teichert
Director, Regulatory Affairs

Dear Ms. Ross-Teichert:

We acknowledge receipt on May 4, 2010, of your May 4, 2010, resubmission to your new drug application for acetaminophen injection.

We consider this a complete, Class 2 response to our February 10, 2010, action letter. Therefore, the user fee goal date is November 4, 2010.

If you have any questions, call me at (301) 796-1232.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
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-22450	ORIG-1	CADENCE PHARMACEUTICA LS INC	Ofirmev (acetaminophen for injection)

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/s/

PARINDA JANI
05/14/2010



NDA 22-450

MEETING MINUTES

Cadence Pharmaceuticals
12481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: Malcolm Lloyd-Smith
Senior Vice President, Regulatory Affairs and Quality Assurance

Dear Mr. Lloyd-Smith:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ofirmev (acetaminophen) Injection, 10mg/mL.

We also refer to the meeting between representatives of your firm and the FDA on April 16, 2010. The purpose of the meeting was to discuss the deficiencies outlined in the complete response letter dated February 10, 2010.

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

If you have any questions, call me at (301) 796-4227.

Sincerely,

{ See appended electronic signature page }

Don L. Henry
Regulatory Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure – meeting minutes



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

Meeting Date and Time:	April 16, 2010
Meeting Type:	Type A
Meeting Category:	Post Review
Meeting Location:	10903 New Hampshire Ave Silver Spring, MD 20993
Application Number:	NDA 22-450
Product Name:	OFIRMEV (Acetaminophen IV)
Received Briefing Package	March 11, 2010
Sponsor Name:	Cadence Pharmaceuticals, Inc.
Meeting Chair:	Prasad Peri, Ph.D.
Meeting Recorder:	Don Henry

FDA ATTENDEES

Office of New Drugs Quality Assessment

Prasad Peri, Ph.D., Acting Branch Chief

Danae Christodoulou, Ph.D., Chemistry Lead (via phone)

Don Henry, Regulatory Project Manager

Office of Compliance

Zi Qiang Gu, Ph.D., Compliance Officer

Office of New Drugs

Sharon Hertz, M.D., Deputy Division Director, DAAP

Office of Regulatory Affairs (via phone)

Kari Batey, Compliance Officer

Marvin Jones, Consumer Safety Officer

James Blakely, Supervisory Consumer Safety Officer

Tony Abel, Pre-Approval Manager

CADENCE PHARMACEUTICALS ATTENDEES

Malcolm Lloyd-Smith, SVP Regulatory Affairs & Quality Assurance
Jim Breitmeyer, EVP and Chief Medical Officer

BAXTER ATTENDEES

Ted Leggett, VP Quality, Medication Delivery

1.0 BACKGROUND

In May 2009, Cadence Pharmaceuticals, Inc submitted a New Drug Application (NDA 22-450) for Acetaminophen Injection for Intravenous Use. On February 10, 2010, a Complete Response was issued. To address the deficiencies identified in the Complete Response letter, Cadence requested a Type A, Post Review Meeting.

2.0 DISCUSSION

- 2.1 **Briefing Package Question 1:** Baxter believes that Observation 1 has been fully addressed, does the Agency concur?

FDA Response:

The manufacturer has not completely addressed all GMP deficiencies in the response to the inspectional observations. More information/documents are needed in order to fully evaluate the adequacy of the response and their corrective actions.

CDER Office of Compliance will work with the DO to communicate with the manufacturer to request more information/documents regarding the corrective and preventive actions the manufacturer has proposed and implemented for evaluation.

Therefore, District Office will provide comments to the manufacturer to request more information for further evaluation to resolve these issues.

Meeting Discussion: The Agency indicated that the responses to the FDA 483 observations for the Baxter Facility are still under review and that the following concerns should be addressed in the response (but not limited to these items):

- What was the source of the foreign matter contamination
- Were all corrective actions implemented and determined to be successful
- Did the corrective actions affect other clean rooms within the facility

Baxter indicated that they have submitted the follow-up responses on March 16, 2010 and March 23, 2010 respectively, including (b) (4) process validation, and the last follow-up item for the response, including re-qualification (b) (4) will be submitted by May 1, 2010. The Agency requested Baxter to provide the results from the validation batches. The results may be submitted as part of the validation summary report, and should include the individual particulate/foreign matter count.

To resolve the observations, Baxter representatives (Contact persons: Ted Leggett or Becky Nowell) should continue to coordinate with the FDA District Office. The Agency indicated that an Establishment Inspection Report (EIR) will not be issued until all open items from the inspection have been closed.

FDA District Office Contact: Kari Batey
Phone number: 615-366-7808
Email: kari.batey@fda.hhs.gov

- 2.2 Briefing Package Question 2:** Baxter believes that Observation 2 has been fully addressed, does the Agency concur?

FDA Response:

See response to question #1.

Meeting Discussion: See meeting discussion to question #1.

- 2.3 Briefing Package Question 3:** Baxter believes that Observation 3 has been fully addressed, does the Agency concur?

FDA Response:

See response to question #1

Meeting Discussion: See meeting discussion to question #1.

- 2.4 Briefing Package Question 4:** Baxter believes that the observations identified by the inspector have been adequately addressed and that the Baxter Cleveland Facility continues to be in satisfactory compliance with cGMP regulations, thus supporting recommendation of approval for NDA 22-450. Does the Agency concur?

FDA Response:

See response to question #1

Meeting Discussion: See meeting discussion to question #1.

- 2.5 Briefing Package Question 5:** Cadence believes that the NDA contains sufficient stability data for the Agency to assign a preliminary shelf life for OFIRMEV at the time of approval. Does the Agency concur?

FDA Response:

We note that updated drug product stability information was provided in an amendment dated January 13, 2010. Please provide any further available data at the time of the NDA resubmission.

We remind you that expiration dating will be assessed upon NDA resubmission, as per ICH Q1E, based on real time, primary and supporting stability data, and statistical analysis evaluation, as applicable.

Meeting Discussion: Cadence indicated that no additional stability data is available at this time.

- 2.6 Briefing Package Question 6:** Assuming Agency agreement with the corrective actions undertaken by Baxter and the positions outlined above, Cadence proposes to immediately resubmit the NDA, composed primarily of revised labeling and a safety update. A Class 1 designation would be requested. Does the Agency concur?

FDA Response:

The Agency will review the information provided in the re-submission upon receipt to determine the Class designation.

Meeting Discussion: Cadence proposed the following re-submission strategies and requested feedback from the Agency in determining which would provide the earliest action, assuming a re-inspection of the Baxter Facility is required.

1. Re-submit the application after issuing all corrective action items for the FDA 483.
2. Re-submit the application after the re-inspection of the Baxter Facility has been completed and found acceptable.

The Agency indicated that the timing of the re-submission must be determined by Cadence, however, the Agency will review all information in a timely manner and would take action when all items from the Complete Response have been adequately addressed, regardless of the established action date.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No other comments

4.0 ACTION ITEMS:

No additional action items were identified during the meeting

5.0 CONCURRENCE:

{See appended electronic signature page}

Don Henry
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6.0 ATTACHMENTS

The following slides were presented by Cadence/Baxter during the meeting:

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	GI-1	CADENCE PHARMACEUTICA LS INC	Ofirmev (acetaminophen for injection)

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/s/

DON L HENRY
04/29/2010

PRASAD PERI
04/29/2010
I concur



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

Meeting Date and Time:	April 16, 2010
Meeting Type:	Type A
Meeting Category:	Post Review
Meeting Location:	10903 New Hampshire Ave Silver Spring, MD 20993
Application Number:	NDA 22-450
Product Name:	OFIRMEV (Acetaminophen IV)
Received Briefing Package	January 11, 2010
Sponsor Name:	Cadence Pharmaceuticals, Inc.
Meeting Chair:	Prasad Peri, Ph.D.
Meeting Recorder:	Don Henry

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled as a **face-to-face meeting** on **Friday, April 16, 2010** from **15:00 – 16:30 ET** between **Cadence Pharmaceuticals Inc**, and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Don Henry, Regulatory Health Project Manager for Quality, 301-796-4227). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

1.0 BACKGROUND

In May 2009, Cadence Pharmaceuticals, Inc submitted a New Drug Application (NDA 22-450) for Acetaminophen Injection for Intravenous Use. On February 10, 2010, a Complete Response was issued. To address the deficiencies identified in the Complete Response letter, Cadence requested a Type A, Post Review Meeting.

2.0 DISCUSSION

- 2.1 **Briefing Package Question 1:** Baxter believes that Observation 1 has been fully addressed, does the Agency concur?

FDA Response:

The manufacturer has not completely addressed all GMP deficiencies in the response to the inspectional observations. More information/documents are needed in order to fully evaluate the adequacy of the response and their corrective actions.

CDER Office of Compliance will work with the DO to communicate with the manufacturer to request more information/documents regarding the corrective and preventive actions the manufacturer has proposed and implemented for evaluation.

Therefore, District Office will provide comments to the manufacturer to request more information for further evaluation to resolve these issues.

- 2.2 **Briefing Package Question 2:** Baxter believes that Observation 2 has been fully addressed, does the Agency concur?

FDA Response:

See response to question #1.

- 2.3 **Briefing Package Question 3:** Baxter believes that Observation 3 has been fully addressed, does the Agency concur?

FDA Response:

See response to question #1

- 2.4 **Briefing Package Question 4:** Baxter believes that the observations identified by the inspector have been adequately addressed and that the Baxter Cleveland Facility continues to be in satisfactory compliance with cGMP regulations, thus supporting recommendation of approval for NDA 22-450. Does the Agency concur?

FDA Response:

See response to question #1

- 2.5 **Briefing Package Question 5:** Cadence believes that the NDA contains sufficient stability data for the Agency to assign a preliminary shelf life for OFIRMEV at the time of approval. Does the Agency concur?

FDA Response:

We note that updated drug product stability information was provided in an amendment dated January 13, 2010. Please provide any further available data at the time of the NDA resubmission.

We remind you that expiration dating will be assessed upon NDA resubmission, as per ICH Q1E, based on real time, primary and supporting stability data, and statistical analysis evaluation, as applicable.

- 2.6 **Briefing Package Question 6:** Assuming Agency agreement with the corrective actions undertaken by Baxter and the positions outlined above, Cadence proposes to immediately resubmit the NDA, composed primarily of revised labeling and a safety update. A Class 1 designation would be requested. Does the Agency concur?

FDA Response:

The Agency will review the information provided in the re-submission upon receipt to determine the Class designation.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No other comments

4.0 CONCURRENCE:

{See appended electronic signature page}

Don Henry
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Prasad Peri, Ph.D.
Acting Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	GI-1	CADENCE PHARMACEUTICA LS INC	Ofirmev (acetaminophen for injection)

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/s/

DON L HENRY
04/13/2010

PRASAD PERI
04/13/2010



NDA 22-450

MEETING REQUEST GRANTED

Cadence Pharmaceuticals
21481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: Tracy Ross-Teichert
Director, Regulatory Affairs

Dear Ms. Ross:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ofirmev (acetaminophen) Injection, 10mg/mL.

We also refer to your March 11, 2010, correspondence requesting meeting to discuss the deficiencies outlined in the complete response letter dated February 10, 2010. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: April 16, 2010
Time: 15:00 – 16:30 ET
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

CDER participants:

Prasad Peri, Ph.D., Acting Branch Chief, ONDQA
Danae Christodoulou, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Martin Haber, Ph.D., Product Quality Reviewer, ONDQA
Colleen Hoyt, Compliance Officer,
Zi Qiang Gu, Ph.D., Consumer Safety Officer
Sharon Hertz, Ph.D., Deputy Director, DARRP
Ellen, Fields, Ph.D., Medical Officer, DARRP
Parinda Jani, Chief Project Manager, DARRP
Tony Abel, Pre-approval Manager, ORA
Don Henry, Regulatory Project Manager, ONDQA

Please e-mail me any updates to your attendees at don.henry@fda.hhs.gov at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Don Henry x64227.

If you have any questions, call me at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Don L. Henry
Regulatory Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	April 16, 2010, 15:00 ET
MEETING ENDING DATE AND TIME	April 16, 2010, 16:30 ET
PURPOSE OF MEETING	To discuss submission following a complete response
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Blg 22, Room 1421
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Don Henry Regulatory Project Manager White Oak Building 21, Room: 2605 301-796-4227
ESCORT INFORMATION (If different from Hosting Official)	Same as above

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

GI-1

CADENCE
PHARMACEUTICA
LS INC

Ofirmev (acetaminophen for
injection)

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/s/

DON L HENRY
03/25/2010

EXEC CAC MINUTES

Executive CAC

Date of Meeting: February 2, 2010

Committee: David Jacobson-Kram, Ph.D., DABT, OND IO, Member
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Dan Mellon, Ph.D., DAARP, Pharm Tox Supervisor
Carlic Huynh, Ph.D., DAARP, Presenting Reviewer

Author of Minutes: Carlic Huynh, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 22-450

Drug Name: Intravenous Acetaminophen

Sponsor: Cadence Pharmaceuticals

To date, there are no drug product labels for acetaminophen products that contain information on the carcinogenic potential of this drug. However, carcinogenicity assessment of dietary acetaminophen has been completed by the National Toxicology Program (NTP-1993) in both rats and mice. NDA 22-450, was submitted in support of an intravenous formulation of acetaminophen (APAP) for the treatment of acute post-operative pain, the results of the NTP studies were evaluated for inclusion in the product labeling.

The NTP-1993 carcinogenicity studies were conducted in compliance with FDA Good Laboratory Practice regulations. An adequate number of rats and mice have been used. In this study, groups of 50 rats and mice of each sex were administered 0, 600, 3000, or 6000 mg/kg (ppm) APAP through the feed for up to 104 weeks. Doses were selected based on the results of 13-week dose range-finding studies that defined a maximum tolerated dose (MTD). At 15 months, 10 rats and mice per sex from each dose group were randomly selected for interim evaluation. The appropriate protocols were used and included histological examinations of various tissues. Statistical analyses included pairwise comparisons and identification of dose-related trends. The studies; therefore, are deemed acceptable to inform product labeling.

Mouse Carcinogenicity Study

In the mouse study, groups of 50 male and 50 female B6C3F1 mice, eight to nine weeks old, were given APAP at concentrations of 0, 600, 3,000, or 6,000 mg/kg (ppm) in food for up to 104 weeks. The NTP Board of Scientific Counselor's Technical Reports Review Subcommittee and associated Panel of Experts reviewed the studies in 1990.

They concluded that that there was no evidence of carcinogenic activity in male and female mice.

Rat Carcinogenicity Study

In the rat study, groups of 50 male and 50 female Fischer 344/N rats, seven to eight weeks old, were given APAP in the diet at concentrations of 0, 600, 3,000, or 6,000 mg per kg (ppm) in food for up to 104 weeks. The NTP Board of Scientific Counselor's Technical Reports Review Subcommittee and associated Panel of Experts concluded that there was no treatment-related increase in tumor incidence was found in male rats and there was equivocal evidence of carcinogenic activity in female rats based on increased incidences of mononuclear cell leukemia.

Regarding the observation of mononuclear cell leukemia in the female F344/N rats, 9/50, 17/50, 15/50, and 24/50 rats were affected by this observation after treatment with 0, 600, 3000, and 6000 mg/kg APAP, respectively (see Table 1). As shown in Table 1 (reproduced from the NTP Technical Report No. 394), only the high dose group was statistically significant compared to control ($P < 0.05$) via pair wise comparison. There was a significant trend analysis for this finding. Finally, the incidence in the high dose animals exceeded the historical control range of 6-40%.

Table 1

Incidence of Mononuclear Cell Leukemia in Female Rats in the 2-Year Feed Study of Acetaminophen^a

	0 ppm	600 ppm	3,000 ppm	6,000 ppm
Overall rates ^b	9/50 (18%)	17/50 (34%)	15/50 (30%)	24/50 (48%)
Adjusted rates ^c	26.4%	42.8%	35.1%	56.3%
Terminal rates ^d	6/30 (20%)	12/34 (35%)	8/34 (24%)	10/28 (36%)
First incidence (days)	575	581	485	554
Life table tests ^e	P=0.003	P=0.116	P=0.188	P=0.003
Logistic regression test ^e	P=0.003	P=0.070	P=0.120	P=0.001

^a 2-year historical incidence for untreated controls at study laboratory (mean): 66/399 (16.5%); 2-year historical incidence for untreated control groups in NTP studies (mean ± SD): 425/2,043 (20.8% ± 8.1%)

^b Number of neoplasm-bearing animals/number of animals examined at site

^c Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

^d Observed incidence at terminal kill

^e Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal.

As noted in the report, arguments against an association of APAP and mononuclear cell leukemia in female rats included that lack of a signal in the male rats, the variability of the background rates for this finding in Fischer rats and the lack of concordance with a lifetime study of APAP in Fischer rats in a study conducted in Japan. According to the NTP-1993 study report, the Board of Scientific Counselors Peer Review Panel elected to change the NTP staff conclusion from “some evidence of carcinogenic activity” to “equivocal evidence of carcinogenic activity.”

Executive CAC Recommendations and Conclusions:

Mouse Carcinogenicity Study

- The committee concurred that there were no drug-related neoplastic findings in male or female mice.

Rat Carcinogenicity Study

- The committee concurred that there were no drug-related neoplastic findings in male rats. There was a statistically significant increase in mononuclear cell leukemia in females at the high dose. The committee noted that this malignancy is common to Fischer rats and is considered of limited relevance to humans. The committee recommended that the labeling of the product describe the results of the studies but note that this is of limited relevance.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\

Division File, DAARP
MellonD/Team leader, DAARP
HuynhC/Reviewer, DAARP
SistaR/CSO/PM, DAARP
ASeifried, OND IO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICA LS INC	Ofirmev (acetaminophen for injection)

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/s/

ADELE S SEIFRIED
02/02/2010

DAVID JACOBSON KRAM
02/04/2010



NDA 022450

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Cadence Pharmaceuticals, Inc.
12481 High Bluff Drive, Suite 200
San Diego, California 92130

ATTENTION: Malcolm Lloyd-Smith
Senior Vice President, Regulatory Affairs and Quality

Dear Mr. Lloyd-Smith:

Please refer to your New Drug Application (NDA) dated May 12, 2009, received May 13, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection, 1000 mg/100 mL.

We also refer to your October 23, 2009, correspondence, received October 26, 2009, requesting review of your proposed proprietary name, Ofirmev. We have completed our review of the proposed proprietary name, Ofirmev and have concluded that it is acceptable.

The proposed proprietary name, Ofirmev, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 23, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Bola Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Ramani Sista at (301) 796-1236.

Sincerely,
{See appended electronic signature page}

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

ORIG-1

CADENCE
PHARMACEUTICA
LS INC

ACETAMINOPHEN FOR
INJECTION FOR IV USE

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/s/

CAROL A HOLQUIST
01/11/2010



NDA 22-450

DISCIPLINE REVIEW LETTER

Cadence Pharmaceuticals
21481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: Tracy Ross-Teichert
Director, Regulatory Affairs

Dear Ms. Ross:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acetaminophen Injection, 10 mg/mL.

The Division of Medical Error Prevention and Analysis (DMEPA) have completed their review of the carton and container labels of your submission, and have identified the following deficiencies:

A. Container Label (1000 mg/100 mL vial)

1. As presented in the revised container labels, the graphic of the [REDACTED] (b) (4) proposed proprietary name, Ofirmev, makes this final letter of the name appear to be part of the graphic rather than part of the name and thus effects the readability of the proprietary name. We recommend revising the graphic as to not interfere with the readability of the proprietary name.
2. The presentation of the proprietary name and the product strength [REDACTED] (b) (4) reduces the prominence of the established name. Revise the presentation of the established name so that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10 (g)(2).
3. Include the following statement following the single use statement on the principle display panel, "Doses less than 1000 mg require aseptic transfer to a separate container prior to dispensing." The storage directions may be relocated to the side panel if space affects the readability of these statements.

B. Carton Labeling (1 x 24 vials)

1. Include the following statement prior to the storage instructions, “Doses less than 1000 mg require aseptic transfer to a separate container prior to dispensing.”

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Ramani Sista, Regulatory Project Manager, at (301) 796-1236.

Sincerely,

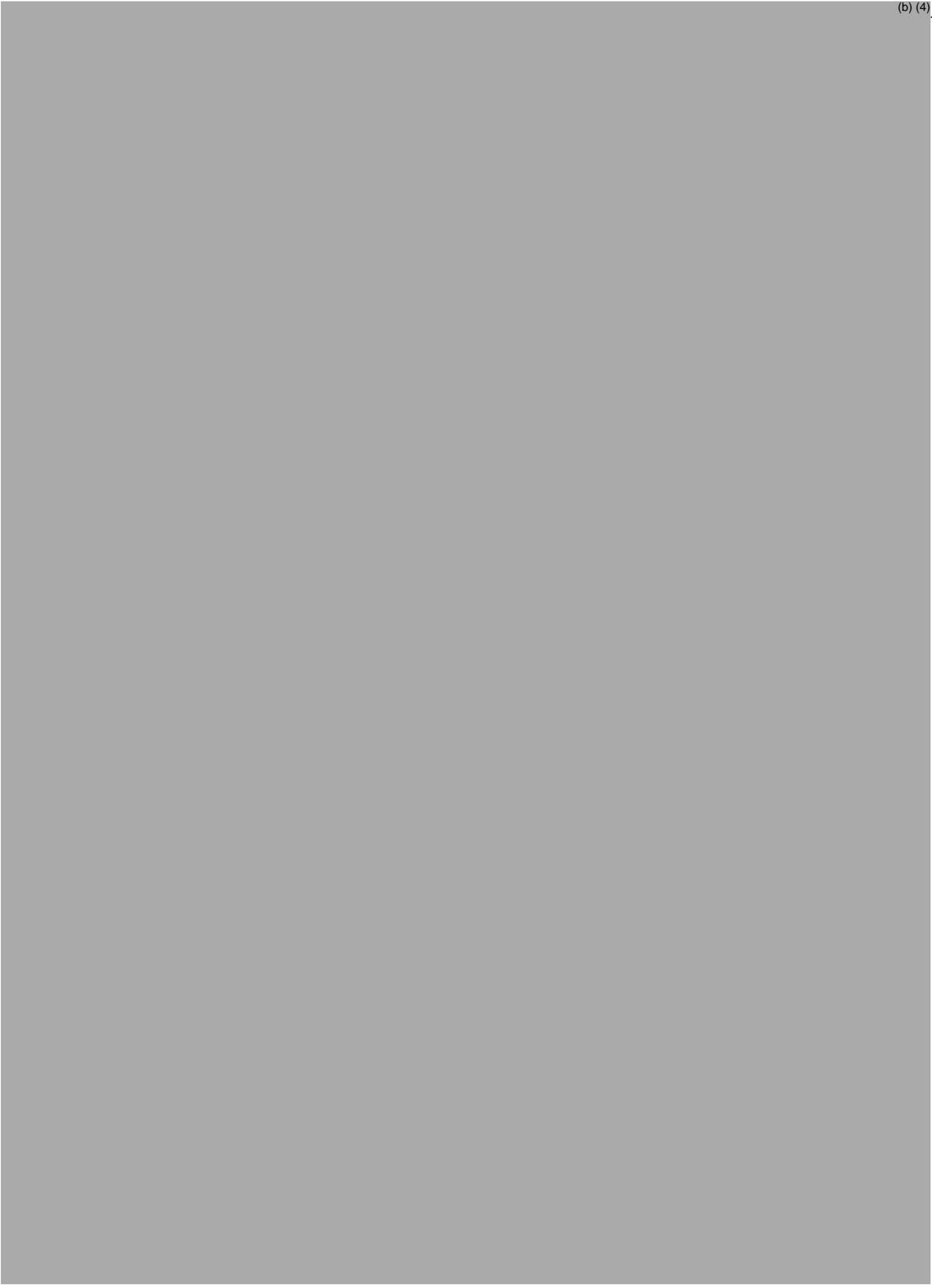
{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Appendices

APPENDICES

(b) (4)



Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

ORIG-1

CADENCE
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ACETAMINOPHEN FOR
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/s/

PARINDA JANI
12/23/2009



NDA 22-450

PDUFA GOAL DATE EXTENSION

Cadence Pharmaceuticals
21481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: Tracy Ross-Teichert
Director, Regulatory Affairs

Dear Ms. Ross:

Please refer to your new drug application (NDA) dated May 12, 2009, received May 13, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACETAVANCE™ (Acetaminophen) intravenous (IV) 10mg/mL.

On November 9, 2009, we received your major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 12, 2010.

If you have any questions, call Ramani Sista, Regulatory Project Manager, at (301) 796-1236.

Sincerely yours,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

ORIG-1

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PARINDA JANI
11/10/2009



NDA 022450

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Cadence Pharmaceuticals, Inc.
12481 High Bluff Drive, Suite 200
San Diego, California 92130

ATTENTION: Malcolm Lloyd-Smith
SVP, Regulatory Affairs and Quality

Dear Mr. Lloyd-Smith:

Please refer to your New Drug Application (NDA) dated May 12, 2009, received May 13, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection 10 mg/mL.

We also refer to your request for a reconsideration of the proposed proprietary name, (b) (4), dated September 14, 2009 and your request for review of the proprietary name (u) (4) dated September 18, 2009.

We acknowledge receipt of your October 23, 2009 correspondence, received on October 26, 2009, notifying us that you are withdrawing your request for reconsideration of the proposed proprietary name (b) (4) and your request for review of the proposed proprietary name (b) (4). These proposed proprietary names requests are considered withdrawn as of October 26, 2009.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Bola Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Ramani Sista at (301) 796-1236.

Sincerely,

{See appended electronic signature page}

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

ORIG-1

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/s/

CAROL A HOLQUIST
11/09/2009



NDA 22-450

DISCIPLINE REVIEW LETTER

Cadence Pharmaceuticals
21481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: Tracy Ross-Teichert
Director, Regulatory Affairs

Dear Ms. Ross:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (Acetaminophen) intravenous (IV) 10 mg/mL.

The Division of Medical Error Prevention and Analysis (DMEPA) has completed their review of the carton and container labels of your submission, and have identified the following deficiencies:

A. General Comments

1. Delete the statement (b) (4) throughout the labels and labeling. The term (b) (4) may imply that the 1000 mg dose is a fixed dose for all patients. However, many patients will receive doses requiring less than 1000 mg of acetaminophen.
2. Present the proprietary name using only one color and one size font. The use of two colors as well as the bolding of only part of the name in the presentation of a proprietary name incorporates similar principles as Tall Man lettering by highlighting and providing prominence to only one portion of the name.

B. Carton Labeling (carton of 24 vials)

1. Revise the presentation of the established name so that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21CFR 201.10(g)(2).
2. Revise the presentation of the strength to appear below the established name and above the route of administration. For example:

(b) (4)

3. Relocate the quantity statement (24 vials) so that it appears in a location away from the product name and strength, preferably near the upper or lower edge of the label.
4. Revise the statement (b) (4) to read “Single Use Vial, discard unused portion.”

C. Container Labels (1000 mg/ 100 mL)

1. Revise the presentation of the established name as noted in Comment B1.
2. Revise the presentation of the strength to below the established name and above the route of administration. (See example in Comment B2 above.)
3. Revise the prominence of the strength presentation so that is it consistent with the proprietary name.
4. Revise the statement (b) (4) to read “Single Use Vial, discard unused portion.”

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Ramani Sista, Regulatory Project Manager, at (301) 796-1236.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

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/s/

PARINDA JANI
10/29/2009

Based on a preliminary review, it appears that the FDA has not yet assigned a pregnancy category to prescription single ingredient acetaminophen product. The Sponsor refers to clinical data in section 2.7.4.5.4 in the submission, however there does not appear to be actual literature references included. Please review the existing clinical data on the use of acetaminophen during pregnancy and provide the Division with references and recommended language pertaining to the clinical components of the proposed pregnancy, labor and delivery, and nursing mothers section of the labeling. Please comment if you believe there are adequate and well controlled clinical studies in pregnant women to inform the pregnancy category designation as per 21CFR201.57.

Please note, this NDA is relying upon the Agency's previous findings of safety and effectiveness for NDA 19-872 (Tylenol) as well as the published literature. Your review should specifically note if the sponsor has referenced any other FDA approved drug product and if so, if that information is necessary to inform your proposed labeling due to patent certification issues associated with the use of data for which the sponsor has not provided adequate patent certification. If your review includes the use of references you have identified, and these references are necessary to inform labeling, you should also include a statement to that effect in order for the Division to determine if there are outstanding patent certification issues that will affect the legal b(2) clearance process. In the absence of clear determination, the recommendations you provide may not be able to be included in the product labeling

The label and referenced sections are in the EDR in eCTD format. We apologize for the short time frame, as the PDUFA date is November 13, 2009. Please contact Ellen Fields if you have any questions.

DAARP Review Team:
Team Leaders: Ellen Fields and Robert Shibuya
Medical Officers: Christina Fang and Jacqueline Spaulding
Pharmacology/Toxicology: Dan Mello (TL), Carlic Huynh (reviewer)
Clinical Pharmacology: Suresh Doddapaneni (TL), Ping Ji (Reviewer)

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

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/s/

RAMANI V SISTA

10/07/2009

From: [Turner-Rinehardt, Sharon](#)
To: ["Tracy Ross-Teichert"](#);
Subject: NDA 22-
450 for ACETAVANCE (acetaminophen) injection: Information Request
Date: Thursday, June 18, 2009 1:17:37 PM

Dear Tracy,

Although you provided the address and responsibility information for Mallinckrodt, we still need a contact name, telephone and fax number. You should provide this information to me as soon as possible.

Also, we have the following clinical information request.

1. Provide the three datasets in .xpt format that contain the complete adverse event data (also including, at a minimum, unique subject identifier, protocol in which the patient was enrolled, basic demographic data such as age, sex, and race, and treatment assignment) for all adults in the randomized, double-blind, placebo-controlled studies. Exclude healthy volunteer studies and open-label studies. One dataset should contain data for all patients, one for patients in repeat-dose studies, and one should contain data for patients in single-dose studies.

2. Re-analyze these pools and provide summary statistics.

I ask that you provide the requested information by Tuesday, June 30, 2009 at 5pm EST. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3193
Silver Spring, MD 20993-0002
Phone: (301) 796-2254
Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

APPEARS THIS WAY ON
ORIGINAL

From: [Turner-Rinehardt, Sharon](#)
To: ["Tracy Ross-Teichert"](#);
cc: ["Malcolm Lloyd-Smith"](#);
Subject: NDA 22-450 for IV acetaminophen - Information Request
Date: Tuesday, September 01, 2009 2:29:24 PM

Dear Tracy,

We have the following information requests.

1. Provide total related substances data for the US-registration batches of the drug substance. Provide a table of the drug substance specifications for this NDA. Reliance upon pharmacopeia standards alone is not adequate for an injectable product. Include limits for total related substances and individual unidentified impurities in the specifications. Tighten the acceptance limits for the carcinogen chloroacetanilide as much as possible.
2. Regarding the compatibility study ARL 01108, visual observation and turbidity measurements alone are not an adequate test for compatibility with infusion solutions. Repeat this study with chemical testing to confirm the stability of acetaminophen during infusion together with commonly used infusion solutions and drugs.

Explain the observed results with the two drugs, diazepam and chlorpromazine HCl, which showed a reaction.

3. Regarding the drug product testing, provide the approximate rate of flow (Rf) of acetaminophen in the TLC system.
4. Justify the proposed (b) (4) acceptance limits for pH, particulate matter and impurities for your proposed Cleveland product vs. product manufactured at

the BMS, Anagni, Italy. Exceeding pH (b) (4) as the upper limit of the pH range is not acceptable since there is no data available for batches manufactured with that high a pH. Set separate acceptance limits for related substances at release and at shelf-life since due to product degradation in solution adequate limits at release must be tighter.

I ask that you provide a response by 1pm (EST) Tuesday, September 15, 2009. If you have any questions regarding this request, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

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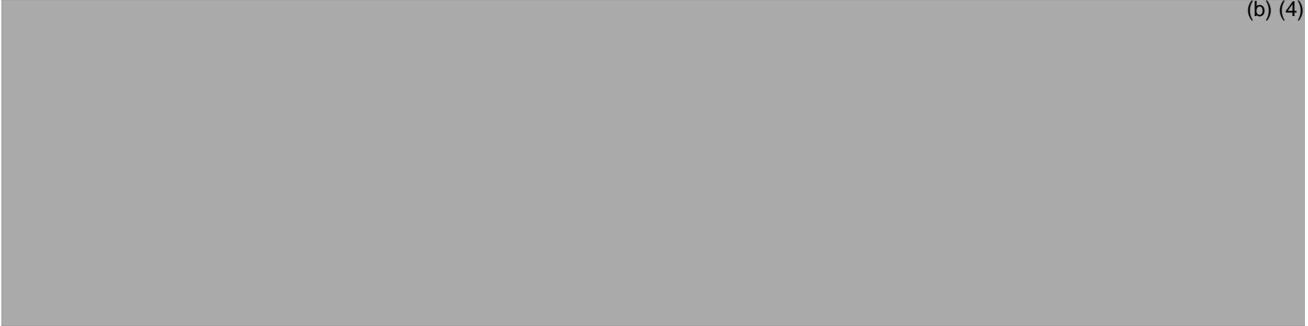
From: [Turner-Rinehardt, Sharon](#)
To: [Malcolm Lloyd-Smith](#);
cc: ["Tracy Ross-Teichert"](#);
Subject: NDA 22-450 for IV acetaminophen - Information Request
Date: Thursday, August 27, 2009 3:50:54 PM

Dear Malcolm,

We have the following information request.

The following is contained in Section 2.4 of the label for IV APAP:

(b) (4)



Clarify why there is language regarding the prevention of an air embolism.

I ask that you provide a response by 1pm (EST) Friday, August 28, 2009. If you have any questions regarding this request, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

From: [Turner-Rinehardt, Sharon](#)
To: ["Tracy Ross-Teichert"](#);
Subject: NDA 22-450 for IV acetaminophen injection: Information Request
Date: Friday, August 07, 2009 1:59:19 PM
Attachments: [Information Request 080709.pdf](#)

Dear Tracy,

Provide the following information for the requested subjects in the attached document. I request that you provide a response by 2 pm, Tuesday, August 11, 2009. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

From: [Turner-Rinehardt, Sharon](#)
To: ["Tracy Ross-Teichert";](#)
Subject: NDA 22-
450 for ACETAVANCE (acetaminophen) injection: Information Request
Date: Wednesday, July 22, 2009 11:53:08 AM

Dear Tracy,

Provide all available information on Patient 001-02, in Study CPI-APA-351, including but not limited to any pre-operative labs (including LFTs), admitting history and physical, hospital progress notes, operative report, and discharge summary.

I ask that you provide the requested information by Tuesday, July 28, 2009 at 3pm EST. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

APPEARS THIS WAY ON
ORIGINAL

From: [Turner-Rinehardt, Sharon](#)
To: ["Tracy Ross-Teichert"](#);
Subject: NDA 22450 Information Request
Date: Wednesday, July 01, 2009 1:14:38 PM

Dear Tracy,
Please provide the fax number as soon as possible for the BMS Anagni facility in Italy.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager

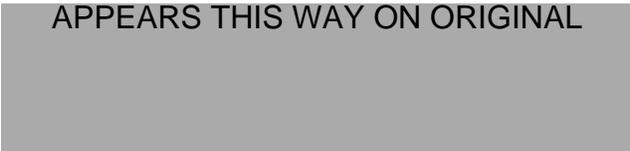
Division of Anesthesia, Analgesia and Rheumatology Products

Phone: (301) 796-2254

Fax: (301) 796-9713

Email: sharon.turner-rinehardt@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL



From: [Turner-Rinehardt, Sharon](#)
To: ["Tracy Ross-Teichert";](#)
Subject: NDA 22-
450 for ACETAVANCE (acetaminophen) injection- Information Request
Date: Wednesday, May 20, 2009 6:46:52 PM

Dear Tracy,

Submit the drug substance manufacturing facility information including the address and responsibilities to the NDA. I ask that you submit this information by 5pm EST, Friday, May 22, 2009. If you have any questions regarding this request, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3191
Silver Spring, MD 20993-0002
Phone: (301) 796-2254
Fax: (301) 796-9713
Email: sharon.turner-rinehardt@fda.hhs.gov

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Application
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Submission
Type/Number

Submitter Name

Product Name

NDA-22450

ORIG-1

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/s/

SHARON M TURNER RINEHARDT
09/28/2009



NDA 22-450

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Cadence Pharmaceuticals, Inc
12481 High Bluff Drive, Suite 200
San Diego, CA 92130

ATTENTION: Tracy A. Ross-Teichert, MSc, RAC
Director, Regulatory Affairs

Dear Ms. Ross-Teichert:

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Injection 10 mg/mL.

We also refer to your August 14, 2009, correspondence, received August 17, 2009, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable from a promotional perspective for the following reasons.



Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i); (e)(6)(i)].

We note that you have proposed an alternate proprietary name in your submission dated August 14, 2009. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Bola Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sharon Turner-Rinehardt, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22450	----- ORIG 1	----- CADENCE PHARMACEUTICA LS	----- ACETAMINOPHEN FOR INJECTION FOR IV USE

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/s/

CAROL A HOLQUIST
09/02/2009

REQUEST FOR CONSULTATION

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

FROM (Name, Office/Division, and Phone Number of Requestor): **Sharon Turner-Rinehardt, RPM /Division of Anesthesia, Analgesia and Rheumatology Products**

DATE
August 20, 2009

IND NO.

NDA NO.
22-450

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
May 13, 2009

NAME OF DRUG
IV Acetaminophen

PRIORITY CONSIDERATION
P

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
October 15, 2009

NAME OF FIRM: **Cadance 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 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <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 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 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

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Cadance has submitted a new NDA for IV Acetaminophen indicated for the treatment of acute pain and fever in adults and pediatrics. Submitted for your review are the proposed package insert (please review the pdf version if you will obtain the label directly from the link) and carton/container labels. The PDUFA date for this NDA is November 13, 2009. If you have any questions, please contact Sharon Turner-Rinehardt, X6-2254.

Submission Link: \\CDSESUB1\EVSPROD\NDA022450\022450.enx (see amendment 10)

10 Pages Draft Labeling have been Withheld In Full as B4 (CCI/TS) Immediately Following this Page

SIGNATURE OF REQUESTOR
Sharon Turner-Rinehardt

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22450	ORIG 1	CADENCE PHARMACEUTICALS	ACETAMINOPHEN FOR INJECTION FOR IV USE
NDA 22450	ORIG 1	CADENCE PHARMACEUTICALS	ACETAMINOPHEN FOR INJECTION FOR IV USE
NDA 22450	ORIG 1	CADENCE PHARMACEUTICALS	ACETAMINOPHEN FOR INJECTION FOR IV USE

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/s/

SHARON M TURNER RINEHARDT
08/20/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): Mail: OSE			FROM: Sharon Turner-Rinehardt, RPM (Jacqueline Spaulding, MO) Division of Anesthesia, Analgesia and Rheumatology Products		
DATE July 28, 2009	IND NO.	NDA NO. 22-450	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT May 12, 2009	
NAME OF DRUG IV Acetaminophen		PRIORITY CONSIDERATION P	CLASSIFICATION OF DRUG Analgesic	DESIRED COMPLETION DATE August 24, 2009	
NAME OF FIRM: Cadence Pharmaceuticals					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
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"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
<p>COMMENTS/SPECIAL INSTRUCTIONS: Acetaminophen (N-acetyl-para-aminophenol) is a synthetic, non-opioid, centrally acting analgesic and antipyretic agent. Although the exact site and mechanism of action of acetaminophen is not clearly known, its effectiveness as an antipyretic is thought to be related to its effect on the hypothalamic heat-regulating center, while its analgesic effect is due to raising the pain threshold.</p> <p>Oral acetaminophen was initially approved by the Agency in 1951 and first marketed in the United States in 1953. In 1960, Tylenol was approved for sale over-the-counter (OTC). Oral acetaminophen has an established efficacy profile, an understood risk/benefit ratio, and at recommended doses is considered safe drug. The significant safety issue associated with acetaminophen is hepatic injury, most commonly after extensive overdose with suicidal intent, but sometimes after accidental overdose, and rarely with therapeutic dosing.</p> <p>Although oral acetaminophen is extensively used as an antipyretic and analgesic, there is no currently parentally administered drug of this class approved for these indications in the United States. The last antipyretic available for parental use was Dipyrone (metamizole) which was withdrawn from the market for safety reasons.</p>					

The safety of acetaminophen has been the subject of considerable discussion in the scientific community, culminating in a joint meeting of the Drug Safety and Risk Management and Anesthetic and Life Support Drugs Advisory Committees in June 2009.

Acetaminophen for injection was approved in France in 2001 and has been marketed as Perfalgan[®] by Bristol-Myers Squibb (BMS) starting in 2002 in most countries; however, other trade names have also been used. In 2006, licensure for North American development and commercialization rights to IV acetaminophen were transferred from BMS to Cadence Pharmaceuticals which has undertaken the drug's development in the United States. Currently, Perfalgan[®] is approved in approximately 80 countries for the same indications of acute pain and fever, both alone and in conjunction with parental opioids and non-steroidal anti-inflammatory drugs, in both adult and pediatric patients.

Cadence Pharmaceuticals has submitted New Drug Application 22-450 for this product (Acetaminophen Injection for Intravenous use). The proposed indication for intravenous (IV) acetaminophen is for the treatment of acute pain and fever in adults and pediatric patients.

The NDA contains copies of nine Perfalgan Periodic Safety Update Reports (PSURs) received from BMS. Cadence has also submitted their own summary review that includes cumulative post-marketing adverse drug reactions of interest from the PSURs and supporting documents from its international birth date June 2001 to January 2009, that represents approximately (b) (4) units of IV acetaminophen distributed and (b) (4) patients.

Given the concerns about the safety of acetaminophen and the substantial amount of foreign postmarketing experience, we are requesting the expertise of the OSE in reviewing the available foreign postmarketing data.

Submission Link:

EDR Location: <\\CDSESUB1\EVSPROD\NDA022450\022450.enx>

If you have any questions, please contact Sharon Turner-Rinehardt, X6-2254.

SIGNATURE OF REQUESTER
Sharon Turner-Rinehardt/072809

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22450	----- ORIG 1	----- CADENCE PHARMACEUTICA LS	----- ACETAMINOPHEN FOR INJECTION FOR IV USE

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/s/

SHARON M TURNER RINEHARDT
07/28/2009



NDA 22-450

FILING COMMUNICATION

Cadence Pharmaceuticals
21481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: Tracy Ross-Teichert
Director, Regulatory Affairs

Dear Ms. Ross:

Please refer to your new drug application (NDA) dated May 12, 2009, received May 13, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for ACETAVANCE™ (Acetaminophen) intravenous (IV) 10mg/mL.

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

1. Your NDA submission does not contain a toxicological risk assessment for the safety of the drug product degradant, 4-aminophenol, which contains a structural alert for genotoxicity and carcinogenicity. As per the published FDA Draft Guidance to Industry, levels of this impurity should be reduced to NMT [REDACTED] (b) (4) unless otherwise justified based on a toxicological risk assessment. In the absence of adequate justification, adequate safety qualification for any potential genotoxic impurities must include:
 - a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies, point mutation assay and chromosomal aberration assay with the isolated impurity, tested up to the limit dose for the assay.
 - b. Should either of these genetic toxicology studies yield positive or equivocal results, the impurity specification must be set at NMT [REDACTED] (b) (4) or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or an appropriate transgenic mouse model.
 - c. Submit a comprehensive toxicological risk assessment for 4-aminophenol by August 13, 2009, which specifically addresses the potential for this compound to contribute to the risk of genetic toxicity, carcinogenicity, reproduction and developmental toxicity and general toxicity (specifically hepatic and renal toxicity). This assessment must include data for the exposures of the animal in your toxicology studies to this impurity via the batches tested and how these levels compare to NOAELs for toxicity.

2. Provide a stability update with updated summary for the primary batches V337108, V337109 and V337112, manufactured at Baxter. In addition, provide a justification for the choice of (b) (4) storage conditions, and a commitment to place post-approval batches on standard ICH long term conditions.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

We note that you have submitted pediatric studies with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

In addition, we have the following comments regarding the labeling submitted in the WORD format with your NDA. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency.

Highlights of Prescribing Information

1. Bold highlights limitation statement “These highlights do not include...”
2. Delete [REDACTED] (b) (4) from the USE IN SPECIFIC POPULATION section.
3. Delete the “TM” after the drug names in Highlights . Use the “TM” symbol only once in the content of labeling (FPI).

Full Prescribing Information (FPI)

4. Consistently indent all paragraphs, headings, subheadings throughout the FPI. For overall formatting, refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for examples of labeling in the new format.
5. In the DOSEAGE and ADMINISTRATION section, removed the bullets from sections 2.1, 2.2, 2.3 and 2.5 and revise in paragraph format.
6. In the DOSAGE FORMS AND STRENGTHS section, remove the bullets and revise in paragraph format.
7. Delete [REDACTED] (b) (4) at the end of the FPI. The revision date at the end of the Highlights replaces this information.

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Health Project Manager, at (301) 796-2254.

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

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/s/

Bob Rappaport
7/22/2009 11:00:17 PM



NDA 22-450

PRIORITY REVIEW DESIGNATION

Cadence Pharmaceuticals
21481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: Tracy Ross-Teichert

Dear Ms. Ross:

Please refer to your new drug application (NDA) dated May 12, 2009, received May 13, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for ACETAVANCE™ (Acetaminophen) intravenous (IV) 10mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. 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 **Priority**. Therefore, the user fee goal date is November 13, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 23, 2009.

While conducting our filing review, if we identify potential review issues, we will communicate them to you on or before July 26, 2009.

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Project Manager, at (301) 796 2254.

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

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/s/

Sharon Hertz
7/13/2009 11:45:25 AM
Signing for Bob Rappaport, M.D.



NDA 22-450

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Cadence Pharmaceuticals, Inc
12481 High Bluff Drive, Suite 200
San Diego, CA 92130

ATTENTION: Tracy A. Ross-Teichert, MSc, RAC
Director, Regulatory Affairs

Dear Ms. Ross:

Please refer to your New Drug Application (NDA) dated May 13, 2009, received May 13, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acetaminophen injection 10 mg/mL.

We also refer to your May 19, 2009, correspondence, received May 20, 2009, requesting review of your proposed proprietary name, Acetavance. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable from a promotional perspective for the following reasons.

(b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or

substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i); (e)(6)(i)].

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Chris Wheeler, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0151. For any other information regarding this application contact Sharon Turner-Rinehardt, the Office of New Drugs (OND) Regulatory Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

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

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/s/

Carol Holquist
6/25/2009 01:02:02 PM



NDA 22-450

NDA ACKNOWLEDGMENT

Cadence Pharmaceuticals
12481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: Malcolm Lloyd-Smith
Senior Vice President, Regulatory Affairs and Quality

Dear Mr. Lloyd-Smith:

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

Name of Drug Product: Acetavance (Intavenous Acetaminophen for Injection)

Date of Application: May 12, 2009

Date of Receipt: May 13, 2009

Our Reference Number: NDA 22-450

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 July 12, 2009, 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable

clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of 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) 796-2254

Sincerely,

{See appended electronic signature page}

Sharon Turner-Rinehardt
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/

Sharon Turner-Rinehardt

5/27/2009 01:52:18 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: ODS		FROM: Sharon Turner-Rinehardt, RPM (Christina Fang/Jacqueline Spaulding, MO) Division of Anesthesia, Analgesia and Rheumatology Products		
DATE May 26, 2009	IND NO.	NDA NO. 22-450	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT May 12, 2009
NAME OF DRUG IV Acetaminophen		PRIORITY CONSIDERATION P	CLASSIFICATION OF DRUG Analgesic	DESIRED COMPLETION DATE August 27, 2009
NAME OF FIRM: Cadence Pharmaceuticals				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Package Insert, Carton/Container Labels, RiskMapp				
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"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Cadence has submitted a new NDA for intravenous acetaminophen (APAP) for injection indicated for the treatment of acute pain and fever. Submitted for your review are the package insert (please review the pdf version if you will obtain the label directly from the link), carton/container labels and risk minimization plan (use link to submission for details of RMP) for this new NDA. A link to the entire submission is provided below and in the calendar notices for the meetings for your reference. If you have any questions, please contact Sharon Turner-Rinehardt, X6-2254.				
<div style="border: 1px solid black; padding: 5px; background-color: #cccccc;"> 21 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page </div>				
SIGNATURE OF REQUESTER Sharon Turner-Rinehardt/010908		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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

/s/

Sharon Turner-Rinehardt
5/26/2009 04:59:36 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **Sylvia Gantt New Drug Microbiology Staff OC/OO/CDER/OPS/NDMS**

FROM (Name, Office/Division, and Phone Number of Requestor): **Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of Danae Christodoulou**

DATE
May 21, 2009

IND NO.

NDA NO.
22-450

TYPE OF DOCUMENT
NDA submission

DATE OF DOCUMENT
May 13, 2009

NAME OF DRUG
Acetavance (Acetaminophen for injection)

PRIORITY CONSIDERATION
priority

CLASSIFICATION OF DRUG
Analgesics

DESIRED COMPLETION DATE
August 30, 2009

NAME OF FIRM: **Cadence 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 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 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

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This product is aseptically processed and (b) (4) sterilized (b) (4) (). Microbiology consultation is requested to review the manufacturing process and specifications. Reference to the Baxter DMF 4681. The NDA is electronic.

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Ali Al-Hakim
5/22/2009 11:24:49 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,362

Cadence Pharmaceuticals, Inc.
12730 High Bluff Drive, Suite 410
San Diego, CA 92130

Attention: Richard E. Lowenthal, MSc
Vice President, Regulatory Affairs

Dear Mr. Lowenthal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen for Injection.

We also refer to the meeting between representatives of your firm and the FDA on August 14, 2006. The purpose of the meeting was to discuss the End-of-Phase 2 development plans to support an NDA.

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) 796-2254.

Sincerely,

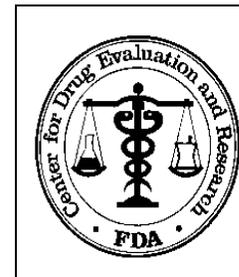
{See appended electronic signature page}

Sharon Turner-Rinehardt
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING AGENDA

Meeting Date: August 14, 2006
Location: White Oak, Building 22, Conference Room 1309
IND/ Name: 58,362/Acetaminophen
Indication: Analgesic for post-operative pain and use as an anti-pyretic in pediatric patients
Sponsor: Cadence
Type of Meeting: Type B (EOP2)
Meeting Chair: Sharon Hertz, MD
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170
Minutes Recorder: Sharon Turner-Rinehardt, RPM



Cadence	Title
Theodore Schroeder	CEO/President
Jim Breitmeyer; MD, PhD	Executive Vice President of Clinical Development and CMO
Mike Royal; MD, PhD, MBA	Vice President Clinical
Richard Lowenthal, MSc	Vice President RA/QA
Wayne Alves	Sr. Director Project Management
Yueh Chang, PhD	Director Biostatistics
Susan Simmons	Director Regulatory Affairs
(b) (4)	
FDA	Title
Curtis Rosebraugh, MD	Deputy Director, ODE II
Bob A. Rappaport, MD	Division Director
Sharon Hertz, MD	Deputy Division Director
Christina Fang, MD	Medical Officer
Ali H. Al Hakim, PhD	Pharmaceutical Assessment Lead
Adam Wasserman, PhD	Supervisor, Pharmacology/Toxicology
Asoke Mukherjee, PhD	Pharmacology/Toxicology Reviewer
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader
Dionne Price, PhD	Acting Team Leader, Statistics
Joan Buenconsejo, PhD	Statistical Reviewer
Janice Weiner, JD, MPH	Regulatory Counsel
Kathleen Davies	Regulatory Project Manager
Cherye Milburn	Regulatory Project Manager
Geri Smith	Regulatory Project Manager
Jason Hartman	Regulatory Project Manager
Allison Meyer	Regulatory Project Manager
Sharon Turner-Rinehardt	Regulatory Project Manager

BACKGROUND:

Acetaminophen is a widely used over-the-counter pain reliever. On August 14, 2006, a meeting was held between Cadence Pharmaceuticals and the Agency to discuss the development plans for intravenous acetaminophen for acute post-operative pain or as an anti-pyretic in a controlled, hospital setting when oral medication cannot be administered.

GENERAL DISCUSSION: Following introductions, the discussion focused on the questions that were included in the July 14, 2006, meeting package for IND 58,362. Prior to the meeting, the Sponsor was provided responses to the questions. The questions are presented below in *italicized* text in the order in which they were addressed at the meeting. Agency responses, prepared prior to the meeting and presented on slides, are **bolded**. Discussion is presented in normal text.

IND 58,362 Questions and Responses

Question 1: Does the Agency agree that this extensive body of data on the oral use of acetaminophen, covering the safety, efficacy and non-clinical evaluations, is relevant and provides supportive data for submission of a proposed 505(b)2 NDA/eCTD submission of IV APAP?

FDA Response:

You may rely upon studies not conducted by or for you and to which you have not obtained a right of reference or use (i.e., published literature or the Agency’s finding of safety and/or effectiveness for a listed drug) to support your non-clinical development program. Non-clinical studies which involve the evaluation of acetaminophen toxicity and which adequately address the potential for mutagenicity and reproductive toxicity will provide sufficient non-clinical supportive data for a 505(b)(2) application. If you intend to rely on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54 and the October 1999 Draft Guidance for Industry “Applications Covered by Section 505(b)(2)” available at <http://www.fda.gov/cder/guidance/guidance.htm> for further information. We also note that should a pharmaceutically equivalent product be approved before your application is submitted, such that your proposed product is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

As a new route of drug administration to be used in a different target population with mostly hospitalized and severely sick patients, efficacy and safety must be supported by the results of clinical studies of the new formulation. The data from the experience with oral

acetaminophen is supportive, but given the higher C_{max} following IV administration, safety must be established through clinical trials.

Discussion: The Sponsor stated that additional non-clinical data required beyond literature references will be summarized in the 505(b)(2) package.

The Sponsor stated they also intended to support the NDA with reference to the Agency's Summary Basis of Approval (SBA) for approved acetaminophen-containing products. The Division advised the Sponsor that SBAs cannot be used as a reference as SBAs are summaries of data contained in NDAs and some of that data may be proprietary and require a right of reference. The Division noted that the Sponsor may rely upon the Agency's finding(s) of safety and efficacy for a listed drug(s), and may reference non-clinical information contained in the approved label(s) of the listed drug(s) relied upon for support. The Division noted that the Sponsor may rely upon the Agency's finding of safety and effectiveness for more than one listed drug. The Sponsor asked if there were any additional non-clinical studies that would be necessary to submit in the NDA. The Division stated that information that would address gaps that are not addressed in the label would be necessary either through conduct of non-clinical studies or reference to data in the published literature. The Division recommended that the Sponsor submit a draft label which references literature.

Post meeting note: After further internal discussion, non-clinical studies will not be required to address gaps in the label though the Sponsor should address these where possible through information obtained from published literature or data in the public domain.

Question 2: Does the Agency agree that the data from IV PPA clinical trials presented in Section 5 of this briefing package provide supportive evidence of the safety and efficacy of IV APAP given the highly similar pharmacokinetic profile of IV PPA and IV APAP?

FDA Response:

The difference in PK characteristics, particularly the higher C_{max} of IV APAP in comparison to the oral formulation, raises concerns that analgesic duration and drug safety may differ. IV PPA has a relatively lower C_{max} than IV APAP. Therefore, safety data from IV PPA are not considered adequate to address safety concerns associated with the high C_{max} of IV APAP.

Discussion: The Sponsor requested further clarification of the Division's expectations for the propacetamol (pro-drug) data. The Division stated that the data could only be used in a supportive role in the safety database of acetaminophen IV, given that propacetamol has a lower C_{max} and AUC compared to acetaminophen. The Sponsor stated that there are a substantial number of patients and longer-term safety data in the propacetamol database. The Division stated that a summary of the safety of propacetamol should be provided with details for any serious adverse events. The Sponsor stated that a summary of propacetamol safety data in ISS will not be integrated with acetaminophen data and the Division concurred that this was acceptable.

The Sponsor asked, if the propacetamol data could support the efficacy of acetaminophen. Propacetamol and acetaminophen were compared in pediatric studies and there was no difference

in the response. The Division stated that propacetamol has never been approved in the US so there is no basis for an efficacy analysis based on non-inferiority.

Question 3: Cadence proposes to use this pivotal trial as one multiple dose study to support efficacy for the treatment of post-operative pain following orthopedic surgery in addition to the clinical development plan proposed in Section 5 of the attached briefing document. Does the Agency agree?

FDA Response:

Yes.

Discussion: There was no further discussion for this question.

Question 4: Does the Agency agree that the ongoing BMS study (CN 145-010) may constitute a second pivotal trial in an orthopedic model for the planned NDA if the results are positive?

FDA Response:

Yes. This 24-hour study may be sufficient as a second trial to complement the data from the 48-hour US trial.

Discussion: There was no further discussion for this question.

Question 5: Does the Agency agree that controlled clinical trial data from previously conducted BMS IV APAP studies, outline in Section 3 of this briefing package, in combination with the proposed additional Cadence studies will provide adequate data to evaluate the efficacy of IV APAP?

Cadence requests Agency input on the acceptability of each of the completed Phase III trials presented in Section 3 of this submission as pivotal trials demonstrating the safety and efficacy of IV APAP.

FDA Response:

Single-dose studies are not considered appropriate to support a finding of efficacy. Multiple-dose efficacy with support for your proposed dosing interval must be demonstrated in at least one 24-hour study and one 48-hour study.

Furthermore, we note that evidence to support the proposed every 6 hour dosing regimen has not been demonstrated in any of the completed studies.

Discussion: The Sponsor asked for further clarification on the Division's requirement for evidence of the proposed dosing regimen of 4 to 6 hours. The Division stated that the study results presented only support duration of up to 3 hours. It is necessary to provide adequate evidence to support the proposed dosing interval.

The Division stated that a reduction in the amount of morphine used alone is not sufficient to support multiple-dose efficacy. The overall risk-benefit must be favorable. The Division asked in what clinical setting this drug would be considered useful. The Sponsor stated that clinicians have told them that it is beneficial as a component of a multimodal approach to analgesia.

The Division stated that, as a known hepatotoxin, it is important to have a thorough understanding of safety with a sufficient exposure in the safety database to be able to consider the risks in the context of the benefits of using this product. The safety database can include data from the multiple-dose efficacy studies of 24 and 48 hours duration as well as additional data from a 5-day open-label study. The Sponsor asked whether 50 patients on study drug for 5 days including adult and pediatric patients is adequate. The Sponsor noted that economics drive an early switch to oral therapy.

Data from European studies can be submitted as part of the safety database if of adequate quality and if the sites can be inspected. The neonatal study data can also be submitted.

Question 6: Does the Agency agree that a single multiple dose pharmacokinetic trial comparing oral acetaminophen and IV APAP in a crossover design in adult healthy volunteers will be adequate to complete the pharmacokinetics and clinical pharmacology sections of the adult section of the labeling for acetaminophen injection?

FDA Response:

Yes

Discussion: See discussion under question 15.

Question 7: Does the Agency agree that in addition to the existing trials, that the proposed Cadence clinical development plan (Section 5 of the briefing document) for IV APAP would provide sufficient evidence of efficacy and safety to obtain a label for acute pain usually in the post-operative setting?

FDA Response:

We recommend that you perform a placebo-controlled, multiple-dose, fever study in adults to study the duration of the antipyretic effect. Multiple-dose safety data may be required for the pediatric population pending multiple-dose PK study results.

Discussion: See discussion under question 15.

Question 8: Does the Agency agree that this dosing regimen is appropriate for further clinical investigation and final product labeling?

FDA Response:

Clinical data from repeated dosing of the product for up to a minimum of 48 hours is required and longer exposure is strongly recommended in order to address the safety concern about the higher peak exposures. Multiple-dose pharmacokinetic data would

provide additional information about whether there is drug accumulation upon repeated dosing.

The proposed dosing regimen of 1000 mg every 4 hours, but no more than 4000 mg/ day leaves a gap in dosing. You must describe what physicians are to do to address this gap in a safe manner.

Discussion: See discussion under question 15.

Question 9:

a) Does the Agency agree that the primary outcome measures for the multiple-dose pivotal trials outlined in the clinical development plan (Section 5 of the briefing document) for IV APAP are appropriate measures of efficacy and are adequate for submission of a 505(b)2 NDA/eCTD?

b) Does the Agency agree with the proposed secondary endpoints for the multiple-dose pivotal trials as outlined in the clinical development plan?

FDA Response:

You must complete an evaluation of the dosing interval, for example, an end of dosing evaluation of pain at 6, 12, 18, 24, 30, 36, 42, and 48 hours; an evaluation of average pain during each dosing interval and information about rescue (time to rescue, percentage taking rescue, and the amount of rescue in each dosing interval and for the entire 48-hour period).

Discussion: The Sponsor requested further clarification of the primary outcome measure and whether time-to-rescue as the primary single-dose endpoint and the SPID24 as the primary multiple-dose endpoint are acceptable. The Division stated that the primary endpoint must encompass an evaluation of analgesic efficacy over the 48-hour study period. Time-to-rescue is used to support dosing interval and does not need to be compared statistically to the comparator. Patient global can be a secondary endpoint. The Division suggested the Sponsor provide a rationale and data as to why a 24-hour endpoint is more appropriate than 48 hours for the evaluation of primary efficacy. The Sponsor stated that a difference in pain is difficult to detect at 48-hours versus placebo. However, starting the evaluation over the first 24 hours after end of surgery would potentially be contaminated by lingering effects of the anesthesia. The Division noted that it was unusual to hear that a product was not expected to be effective for the first 24 hours after surgery, but would be effective for the second 24-hour period, and then not beyond that time. There would need to be support for a product that could only be expected to be effective in this manner.

The Division also emphasized the importance of evaluating duration by measuring the end of dosing effects.

The Sponsor stated that they will reconsider the design of the study.

Question 10: Does the Agency agree that the proposed safety database and prospective Phase III program (safety/efficacy and PK trials) will provide adequate safety data to support submission of a 505 (b)2 application for the indication of acute pain usually in the post-operative setting in the adult population?

FDA Response:

The predicted safety database appears to be adequate in terms of total exposure. The requirement for multiple-dose exposure will depend, in part, on the results of multiple-dose PK data and any safety signal identified in completed clinical trials and will be based on the number of completers of 24-hour and 48-hour dosing. Longer dosing exposure is strongly recommended.

Discussion: See discussion under question 15.

Question 11: Does the Agency agree that longer term safety data is unwarranted given the extensive clinical trial safety data base and post-marketing experience in the European Union?

FDA Response:

Long-term exposure for more than 48 hours might be required if PK data suggest drug accumulation upon repeated use.

Discussion: See discussion under question 15.

Question 12: Does the Agency agree that a pharmacokinetic study, such as that outlined in the Cadence clinical development plan, would be adequate to provide appropriate dosing information for pediatric use to be included in the IV APAP label?

FDA Response:

An appropriately designed PK study in pediatrics may potentially yield information that can help to inform dosing. Data from clinical trials will be required to support the dosing language.

Discussion: See discussion under question 13.

Question 13: Does the Agency agree with this proposal to evaluate IV APAP in the pediatric population and file these to an NDA for IV APAP?

FDA Response:

Single-dose exposure is reported in more than 200 pediatric patients. Bridging PK information between adult and pediatric populations or a multiple-dose PK comparison between IV and oral formulations in a pediatric population would be helpful. Multiple-dose safety data should be obtained to support safe use in pediatric patients.

Discussion: The Sponsor wanted further clarification whether the proposed studies were enough to support (b) (4) the pediatric population. The Division stated there was concern

with the interpretation of the results of the pediatric studies where PPA was the only control and acetaminophen did not perform statistically better than PPA. As noted, a non-inferiority trial against a product not approved in the US is not considered an adequate and well-controlled trial. The pediatric study requirements need further internal discussions.

Post meeting note: Multiple-dose safety data in appropriate pediatric populations will be required as long as the relative PK of parenteral acetaminophen and oral acetaminophen are different in these patients. Efficacy may be supported to an extent based on the similarity of the PK characteristics. However, as with adult patients, if the PK curve is shifted to the left in pediatric patients, adequate efficacy and safety in pediatric patients must be supported through clinical trial data rather than by bridging to prior findings of efficacy with the oral product.

A Pediatric Written Request may be requested.

Question 14: Does the Agency agree with the proposed labeled indication [REDACTED] (b) (4)
[REDACTED]
[REDACTED]?

FDA Response:

Since acetaminophen is widely used as an analgesic and antipyretic in both adult and pediatric populations, provide a rationale for why the same indications are not suitable for both populations.

Discussion: There was no discussion for this question.

Question 15: Does the Agency believe that [REDACTED] (b) (4)
[REDACTED] *is acceptable wording for inclusion in the product label section on Dosing and Administration?*

FDA Response:

The 4-hour dosing must be supported by clinical data. The more frequent exposure to the higher Cmax is a potential safety concern.

Discussion: The Sponsor provided a hand-out that outlined the proposed efficacy studies with IV acetaminophen. The Sponsor stated that, the exposure of the multiple-dose study was 24-hours because after 24-hours steady-state was achieved. The Sponsor proposed safety studies up to 5 days and asked whether this would be adequate data. The Division stated that this would be considered adequate provided that the 5-day exposure data included an assessment for hepatotoxicity. A shorter time period may be acceptable with this data. The Sponsor stated that previous 24-hour data with patients who were dosed with 4 g/day showed no evidence of LFT elevation.

The Sponsor stated that the formulation is approved in 54 countries. The Division asked the Sponsor to submit the approved labeling.

The Sponsor stated that their overall development plan included an adult fever study and 2 safety studies with flexible-dosing for up to 5 days, and wanted to clarify with the Division if these studies would provide an adequate database. The Division stated that longer-term (more than 48-hour) exposure data should be collected and will discuss further internally as to the number of patients required.

Post meeting note: We have reviewed our meeting minutes from prior meetings. The safety database for adults should include a minimum of 300 patients. Fifty patients on study drug for 5 days, pediatric and adult, are acceptable as a minimum as long as additional data is sought for all patients who can be dosed with the product beyond the efficacy period. If you consider it unsafe for patients to receive this product beyond a specific duration of time, provide an argument to support this and the safety database can be adjusted accordingly. In addition, we note that a number of exposures of pediatric patients had not been agreed upon previously. A minimum of 300 pediatric exposures should be included in the safety database.

Question 16: Cadence does not propose to undertake studies in the patient population with renal and hepatic impairment and proposes to utilize the warnings and precautions of oral acetaminophen as the basis for the final product labeling. Does the Agency concur?

FDA Response:

The professional label contains only an alcohol warning and the statement that
(b) (4) Available information from recent publications
in patients with renal and hepatic impairment should also be considered as part of the
proposed approach to labeling in the warnings and precautions sections.

Discussion: There was no further discussion for this question.

Question 17: Does the Agency agree that formal human cardiovascular safety trial are not necessary to provide appropriate guidance of the potential for cardiotoxicity in the final product labeling for IV APAP?

FDA Response:

Yes.

Discussion: There was no further discussion for this question.

Question 18: Does the Agency agree that given the extensive experience already gained by the medical community with regard to use of oral acetaminophen as monotherapy and in combination with other medications, and from the controlled trails of IV PPA and IV APAP, that additional drug-drug interaction studies are not necessary for approval in the United States and that current labeling language utilized in approved products containing acetaminophen may serve as the basis for the IV APAP labeling?

FDA Response:

Yes. However, available information from recent publications in this area should also be considered as a part of proposed approach.

Discussion: There was no further discussion for this question.

Question 19: Does the Agency agree with the approach to developing a Risk Management Plan outlined in Section 6 of the attached briefing package?

FDA Response:

We generally agree with the approach of developing a Risk Management Plan to address the potential for excessive acetaminophen dosing, however, submission of a complete risk management proposal or RiskMAP will be necessary to determine whether the proposed program is acceptable. When you submit the RiskMAP, you are encouraged to include a background section which outlines the rationale for the program. Additionally, provide the overall goals and objectives of the risk management program and which elements would be implemented to achieve those goals and objectives and how they would achieve them. A rationale for each element of the proposed RiskMAP should be included. The submission should also include a plan to evaluate efficacy of the proposed RiskMAP.

The risk management plan must be finalized at the time of NDA submission.

You are encouraged to review the most recent publicly available information on CDER's views on RiskMAPs. Please refer to the Guidance for Industry Development and Use of Risk Minimization Action Plans and the Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at <http://www.fda.gov/cder/guidance/6358fml.htm> and <http://www.fda.gov/cder/guidance/6359OCC.htm>

Discussion: There was no further discussion for this question.

CMC Comments:

Provide the following CMC information:

- Particulate matters in injections (USP test method <788>)
- Compatibility studies between the drug product and the components of the container closure (infusion) [REDACTED] (b) (4)
- Compatibility studies between the drug product and the proposed diluents used for infusion [REDACTED] (b) (4).
- Stability test data from the above studies

- A well documented pharmaceutical development report as per ICH-Q8
- Sufficient amount of satisfactory stability data to support the proposed expiry dating
- Names, addresses and CFN numbers of all sites involved in manufacturing, testing, packaging and labeling of the drug substance and the drug product

Discussion: There was no further discussion for this comment.

Action Items for IND 58,362:

The Sponsor will:

1. Assess labeling for references to support non-clinical development plan.
2. Provide gap analysis from studies that are not addressed in label.
3. Summarize propacetamol information in ISS from acetaminophen data including serious adverse events.
4. Reassess requirements for long-term dosing.
5. Provide data to show risk benefit for intravenous acetaminophen use.
6. Clarify anticipated use of intravenous acetaminophen and provide rationale for endpoint.
7. Submit European label with current formulation.

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

/s/

Sharon Turner-Rinehardt

9/13/2006 04:51:13 PM

505(b)(2) ASSESSMENT

Application Information		
NDA # 22450	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Ofirmev Established/Proper Name: Acetaminophen Solution Dosage Form: Injection Strengths: 10mg/mL		
Applicant: Cadance Pharmaceuticals, Inc		
Date of Receipt: 05-13-09 RS 5-4-10		
PDUFA Goal Date: 11-4-10		Action Goal Date (if different):
Proposed Indication(s): Treatment of acute pain and fever in adults and pediatrics.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature references	Basic pharmacology, ADME, genetic toxicology, reproductive and developmental toxicology and carcinogenicity.
Tylenol ER/NDA 19-872	label

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

As an intravenous formulation, the bioavailability is 100% by definition. Hence, there is no need to bridge to the approved products that are for oral administration. The sponsor conducted clinical pharmacology studies to demonstrate that pharmacologically relevant plasma concentrations were reached with their formulation.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
If “NO”, proceed to question #5.
If “YES”, list the listed drug(s) identified by name and answer question #4(c).

Tylenol (The review team is still verifying this information.)

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO
If “NO,” proceed to question #10.

Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Tylenol	19-872	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 6) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph: Acetaminophen

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to

section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 8) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a change in dosage form, from oral to intravenous.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 9) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO X

If “NO” to (a) proceed to question #11.

If “YES” to (a), answer (b) and (c) then proceed to question #12.

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

*If “YES” to (c) **and** there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If **“NO”** or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

10) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If **“NO”**, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

11) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 12) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 13) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- X 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

14) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

- YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Jani, Parinda

Subject: FW: NDA 22-450 (IV acetaminophen) - cleared for action (again)

From: Duvall Miller, Beth A
Sent: Wednesday, October 13, 2010 1:44 PM
To: Jani, Parinda
Cc: Quaintance, Kim M; Ripper, Leah W
Subject: NDA 22-450 (IV acetaminophen) - cleared for action (again)

Hi Parinda,

We discussed this application at yesterday's 505(b)(2) clearance meeting and it is cleared for action (again) from a 505(b)(2) perspective.

If you are indeed heading towards approval, please make sure the following corrections are made to the 505(b)(2) assessment before archiving in DARRTS (note that these may have already been done as they were communicated to the RPM during the previous clearance cycle (see my 2/1/10 email below). Here they are again for your convenience:

Q2: specify Tylenol ER tablets, NDA 19-872 in the table. Also, reviewer(s) should document clearly in their reviews that there is no reliance on the TFM for Tylenol.

- Q4b: should be 'no' according to your 11/16/09 email; 4c should then be left blank.
- Q14: deselect "no patent certifications required ..." and select "no relevant patents".
- Note also that the division should address in the relevant review(s) why the known exposure/dosing of Tylenol ER provides necessary information to support the approval of the IV product.

Thanks,

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team

CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

From: Jani, Parinda
Sent: Wednesday, May 26, 2010 11:16 AM
To: Duvall Miller, Beth A
Subject: FW: NDA 22-450 (IV acetaminophen) - cleared for action

Hi Beth:

Cadence Pharmaceuticals have resubmitted NDA 22450 for APAP Injection. I have revised the 505(b)(2) assessment as per your recommendations. The due date is going to be

Reference ID: 2858345

10/19/2010

11/4/2010. Let me know if you need any additional information.

Thanks

Parinda

Beth

Beth Duvall-Miller

Team Leader, Regulatory Affairs Team
CDER/Office of New Drugs

Direct Phone Number: (301) 796-0513

OND IO Phone Number: (301) 796-0700

Fax: (301) 796-9855

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

/s/

PARINDA JANI
11/01/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22450 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Ofirmev Established/Proper Name: acetaminophen Dosage Form: Injection Strengths: 10 mg/mL		
Applicant: Cadence Pharmaceuticals, Inc Agent for Applicant (if applicable):		
Date of Application: May 13, 2009 Date of Receipt: May 13, 2009 Date clock started after UN:		
PDUFA Goal Date: November 13, 2009 (clock extended to February 13, 2010)		Action Goal Date (if different): February 10, 2010
Filing Date: July 12, 2009		Date of Filing Meeting: June 22, 2009
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): Treatment of acute pain and fever		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 58,632				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.				
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
 <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:			X		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			Some of them. PWR to be revised to exclude the studies already submitted
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): August 14, 2006 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 22, 2009

BLA/NDA/Supp #: 022450

PROPRIETARY NAME: Ofirmev

ESTABLISHED/PROPER NAME: acetaminophen

DOSAGE FORM/STRENGTH: Injection 10 mg/mL

APPLICANT: Cadence Pharmaceuticals, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of acute pain and fever

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sharon Turner-Rinehardt Ramani Sista Parinda Jani	Y N N
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Ellen Fields, MD		
Clinical	Reviewer:	Christina Fang Jacqueline Spaulding	Y Y
	TL:	Ellen Fields	N
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

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APPEARS THIS WAY ON ORIGINAL



Clinical Pharmacology	Reviewer:	Ping Ji	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	David Petullo	Y
	TL:	Thomas Permutt	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carlie Huynh	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Danae Christodoulou	Y
	TL:	Ali Al-Hakim	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
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APPEARS THIS WAY ON ORIGINAL



<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<input type="checkbox"/> Not Applicable X YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable X YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable X YES <input type="checkbox"/> NO X YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Sharon Hertz, M.D. Deputy Director	
21st Century Review Milestones (see attached) (optional):	
Comments: None	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22450

ORIG-1

CADENCE
PHARMACEUTICA
LS INC

Ofirmev (acetaminophen for
injection)

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

/s/

PARINDA JANI

05/26/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022450 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Ofirmev Established/Proper Name: Acetaminophen Dosage Form: Injection		Applicant: Cadence Pharmaceuticals Agent for Applicant (if applicable):
RPM: Parinda Jani		Division: DAAP/HFD-170
<p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s): NDA 19-872/Tylenol Oral</p> <p>Provide a brief explanation of how this product is different from the listed drug. Injectable formulation</p> <p>If no listed drug, explain. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 11/01/2010</p> <p><u>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.</u></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>11-02-10</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR February 10, 2010
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

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.

❖ Application Characteristics ²		
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p>Comments:</p>		
BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies		
REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required		
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)		<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)		<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)		
• Office of Executive Programs (OEP) liaison has been notified of action		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated		<input 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 Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

❖ Copy of this Action Package Checklist ³	11-2-10
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR/2-10-10
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	5-4-10
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	5-13-09
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	5-19-10
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	1-11-10 6-5-09/8-28-09/
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 10-6-09/12-17-09/1-8-10/9-15-10 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 10-27-09 <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>)	5-26-10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) 10-13-10
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Not a (b)(2) 10-13-10
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>10-7-09/10-27-10</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<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
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

❖ Internal memoranda, telecons, etc.	included
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg 4-16-10
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 9-13-06
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2-10-10, 11-2-10
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2-9-10
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	10-13-09/10-24-09
• Clinical review(s) (<i>indicate date for each review</i>)	
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	clinical rvw/p11 10-23-09
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 2-10-10
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 10-7-09

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/25/10

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 type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 10-14-09 (2)
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-8-10/1-22-10
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)		<input type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 2-10-10
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None 11-3-09/2-10-10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)		<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)		<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None 2-4-10 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 10-19-09/2-10-10
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None 10-15-09/9-22-10
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 7-9-09/10-13-09
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)		<input 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>)	CMC/10-15-09
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 10-26-10 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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

/s/

PARINDA JANI
11/02/2010



IND 58,362

Rich Cuprys
Senior Director, Regulatory Affairs
Bristol-Myers Squibb Company
Worldwide Consumer Medicines & Specialty Pharmaceuticals
1350 Liberty Avenue
Hillside, NJ 07205-6050

Dear Mr. Cuprys:

Please refer to the meeting between representatives of your firm and FDA on November 14, 2003. The purpose of the meeting was to obtain Division's guidance on Sponsor's revised Clinical Development Plan and Pharmacokinetic Studies.

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}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE: November 14, 2003

TIME: 2:15 pm

LOCATION: Corporate Boulevard, HFD-550, S-300 (site of teleconference)

APPLICATION (DRUG): IND 58,362, Serial #021 (Acetaminophen Injection)

SPONSOR: Bristol-Meyers Squibb Pharmaceuticals

TYPE OF MEETING: Guidance on the revised clinical development plan

MEETING CHAIR: Lee Simon, MD

MEETING RECORDER: Mr. Paul Z. Balcer

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Brian E. Harvey, MD, PhD	Deputy Director, ODEV	ODEV/DAAODP, HFD-550
2. Lee Simon, MD	Division Director	ODEV/DAAODP, HFD-550
3. Joel Schiffenbauer, MD	Medical Officer Team Leader	ODEV/DAAODP, HFD-550
4. Christina L. Fang, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
5. Tatiana Oussova, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
6. Chandra Chaurasia, PhD	Biopharmacology Reviewer	ODEV/DAAODP, HFD-550
7. Carmen DeBellis, RhP	Chief, Project Management	ODEV/DAAODP, HFD-550
8. Paul Balcer	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Michael Bozik, MD	President, Research & Development	Bristol-Meyers Squibb Pharmaceuticals
2. Rich Cuprys	Senior Director, Regulatory Affairs	Bristol-Meyers Pharmaceuticals
3. Howard Hoffman, MD	Executive Medical Director, Medical Development	Bristol-Meyers Squibb Pharmaceuticals
4. Laureen MacEachern, PhD, MPH	Medical Director, Clinical Research	Bristol-Meyers Squibb Pharmaceuticals
5. Jonathan Deutsch, MD	Medical Director, Medical Development	Bristol-Meyers Squibb Pharmaceuticals
6. Jean Battikha	Associate Director, Biostatistics and	Bristol-Meyers Squibb

	Data Management	Pharmaceuticals
7. Donna Coughlin	Associate Director, Regulatory Affairs	Bristol-Meyers Squibb Pharmaceuticals

PURPOSE OF THE MEETING: To obtain Division guidance on Sponsor's revised Clinical Development Plan and Pharmacokinetic Studies.

MEETING OBJECTIVES: To obtain Division feedback on proposed clinical development plan.

QUESTIONS:

Question 1: Does the Agency agree that the PK studies outlined in this clinical plan are sufficient to characterize the pharmacokinetic profile of Acetaminophen Injection?

Initial FDA Response:

The Division has long-term safety concerns about higher peak levels at steady states and the different pattern of drug release (in comparison to oral formulation) after repeated use. The Sponsor should obtain also multiple dose PK data.

Meeting comments:

Multiple-dose PK data.

The Sponsor indicated that multiple-dose PK data, including peak levels at the steady-state, will be obtained from the target population (post-surgical). The blood samples will be collected using a population PK approach. PK study protocol will be submitted for comments.

Question 2: Does the Agency agree that the proposed program, as well as additional safety data available from completed studies and PSURs, will provide adequate safety to support the approval of Acetaminophen Injection?

Question 3: Assuming that the results of the studies support the efficacy and safety of Acetaminophen Injection for the proposed indications, does the Agency agree that the proposed clinical program will fulfill the NDA requirements for this product?

Initial FDA Response (Combined response to Question 2 and 3):

1. Target population/Efficacy.

Since this is a parenteral formulation, it will need to be studied in situations of both in-patient and out-patient surgical settings. Therefore, the target population needs to be clearly identified and studied during the IND. Since acetaminophen alone is not expected to be capable of relieving the level of pain in an in-patient post-surgical setting, it will need to be studied with opioids as background therapy. The Sponsor is reminded that the single dose (A), first day (B) and multiple-dose (C) components for this analgesic need to be established in at least two (i.e. replicate) studies both with and without opioids in the settings noted above. Therefore, it would appear that the minimum number of studies would be 10 studies, not the 8 currently outlined to obtain

replicate evidence for the ABC components of this analgesic in an acute setting. Also, the Sponsor will need to address the Minimal Clinically Important Difference or MCID of this analgesic in the IND studies.

Meeting comments:

Target population/pain models.

The Sponsor proposed of using both outpatient and inpatient post-surgical pain models to study single-dose effects and only inpatient post-surgical pain models to study multiple-dose effects because of the anticipated quick discharge of patients after the surgery in an outpatient setting.

The Minimal Clinically Important Difference (MCID)

The Sponsor is suggested to explore and propose the reasonable parameters (onset, pain scores, and duration) and criteria to define MCID instead of using limited sample size to define MCID.

Because pain response and effect size are model dependent, the criteria for MCID need to be defined with respect to pain model.

2. Safety

Initial FDA Response:

Drug safety is a particular concern of acetaminophen IV formulation because of the associated higher C_{max} (with respects to oral formulation) and the potential use of the formulation in a hospitalized debilitated elderly patient population already at a higher risk for drug-induced hepatotoxicity. Based on the safety data from the controlled clinical trial RC 2103 002 (refer to table below) 6 of 99 (6%) patients on active drugs had liver enzyme elevation in comparison to 1 of 52 (2%) patients on placebo after only 4 doses (administered every 6 hours) of treatment. Even after excluding the 2 subjects in the active treatment groups whose liver Adverse Event (AE)s were considered unlikely to be drug related, the comparison of liver AE between the active treatments and placebo is still 4% to 2 %, a very significant finding in a small trial of such a short duration.

The 4-hour dosing interval between the first and the second dose was originally proposed to answer the question about the single-dose duration that is insufficient to support the proposed every 6 hour dosing interval. However, the 2 grams of acetaminophen to be received in 4 hours precipitate additional safety concerns after reviewing the recently submitted clinical trial safety data from every 6 hour dosing as discussed above.

Longer-term safety on repeated exposure to the higher C_{max} in patients at increased risks (e.g., hemodynamically compromised patients) is one of the major concerns. Safety on extended use should be studied for at least 1 week to 10 days and patients should be followed for at least 30 days. Subpopulations at higher risks for acetaminophen induced hepatotoxicity should be identified and studied. Restricted distribution of the drug may be necessary to reduce risks associated with off-label use.

Table. Liver AEs reported in 7 cases of the 151 subjects treated by 4 doses

Subject	Drug	↑GGT	↑ALT	↑AST	↑Alk. Phos.	Outcome
72 male	Acetaminophen	to 112 in 8d	to 75 in 8d			Resolved in 20d
82 male	Acetaminophen	9 to 27, 3x in 3d	12 to 137, 11x in 3d	25 to 360, 14x in 3d		Cardiac arrest
70 female	Propacetamol		42 to 116, 2.8x in 4d			Resolved
37 female	Propacetamol			78 before taking drug		Resolved
64 male	Propacetamol	58 to 143, 2.5x in 40d			93 to 145, 1.5x in 36d	Stabilized
49 female	Propacetamol	30 to 142, 4.7x in 5d	26 to 52, 2x in 43d		86 to 144, 1.7x in 43d	Resolved
46 male	Placebo	85 to 183, 2x in 5d				Resolved in 35d

Meeting comments:

Acetaminophen is known to be associated with liver toxicities. Whether the toxicities are mainly due to the level of exposure, the duration of exposure, or the combination of the two, had not been systematically studied in the past. Safety information from the 4 completed trials submitted in the current package does not provide details to allow an adequate initial assessment. However, the findings such as the increase of ALT to greater than three times of upper limit of normal range (ULN) in 2 subjects and to almost 3X of ULN in one subject, in such a small sample (99 subjects in the active treatment arm) who received only 4 doses (one day exposure) of IV acetaminophen, did indicate a strong need for a larger safety database with more subjects exposed to the maximum recommended dosage for a longer continuous exposure.

The Sponsor proposed the longer-term safety database to include IV dosing for a couple days followed by oral switch and to include PRN (as needed) dosing. The Division clarified that the longer-term safety database is required for IV formulation on a regular dosing schedule for at least a week in at least 300 patients. The safety data on IV to oral switch are considered helpful but not by themselves meeting the requirements. Patients hospitalized for prolonged IV support or patients under palliative care, who need analgesics but could not take or tolerate oral medication, may be studied.

Hemodynamically unstable population refers to patients with volume depletion after excessive blood loss in a post surgical setting.

The effects of the decreased renal and hepatic blood flow on drug metabolism, distribution, and clearance and the adverse effects of the increased exposure in the population, all need to be considered. The Sponsor suggested that there may be less hepatotoxicity associated with acetaminophen IV formulation because of the bypass of the first-pass drug metabolism. The Division recommended the Sponsor to submit data to support the hypothesis.

The Sponsor proposed to study the formulation in patient with elevated liver enzymes. The Division considers the special population study in selected patients with liver impairment useful in providing information on dosing modification and safety warnings/precautions.

Risks associated with prolonged off label use is a concern especially if there is a safety signal with repeated exposure to higher peak levels (with respect to oral formulation).

The Sponsor needs to provide sufficient safety database and identify the risks associated with the use of IV formulation of acetaminophen in the target population and high-risk population in the NDA database prior to planning for risk management. The ODS will be consulted with regard to the future risk management plan.

Minutes Preparer: Paul Z. Balcer

Chair Concurrence: Brian E. Harvey, MD, PhD, Acting Division Director

Drafted by: PBalcer

Initialed by: BHarvey

Final: 1/15/04

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

/s/

Brian Harvey

1/15/04 04:53:38 PM

MEMORANDUM TO FILE OF TELECON

DATE: July 16, 2003

APPLICATION NUMBER: IND 58,362 (Acetaminophen Injection)

BETWEEN:

Rich Cuprys, Senior Director, Regulatory Affairs
Howard Hoffman, M.D., Executive Medical Director
Jean Battikha, Associate Director, Biostatistics and Data Management

Representing: Bristol-Meyers Squibb Pharmaceuticals
Phone: 908-851-6216

AND

Dr. Lee Simon, Director
Dr. James Witter, Medical Team Leader
Dr. Christina Fang, Medical Reviewer
Hamid Amouzadeh, Ph.D., Pharm/Tox Reviewer
Carmen DeBellas, R.Ph., Chief, Proj. Mgt.

Representing:
The Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Subject:

The purpose of the teleconference was to respond to the Sponsor's question about whether the two 24-hour multiple-dose efficacy studies could be conducted concurrently with the single dose PK/PD trial.

Discussion Points:

- The Division indicates that it is considered acceptable to have the efficacy and PK/PD studies conducted in parallel.
- The Division considers that the potential pain models for studying acetaminophen injection could be two-tiered:
 - The kind of post-operative pain that does not require strong analgesics, where the analgesic effect of acetaminophen could be studied alone.
 - The kind of post-operative pain that usually requires strong analgesics, where the effect of acetaminophen needs to be studied in conjunction with opioids.
- The Division suggests the Sponsor to explore a broad spectrum of pain models to show how the drug could benefit the subpopulations that require IV analgesics in different settings.
- The Division advises the Sponsor to submit their detailed drug development plan for review to get a timely feedback.
- The Division encourages the Sponsor to explore the methodology for studying analgesic onset.
- The Division stated that the clinically relevant efficacy data could be included in the clinical trial description section to inform the labeling.

- The Division recommends the Sponsor to also study the hemodynamically compromised patients (the subpopulation for which an IV analgesic is likely to be used) to better inform drug safety.

Carmen DeBellas, Chief, Project Manager

Dr. James Witter, Medical Team Leader

cc:

Archival IND 58,362

HFD-550/Division Files

Drafted by: NH/10-2--03

Initialed by: jw 10-10-03

Filename:

TELECON

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

/s/

Nancy Halonen
10/14/03 06:42:26 AM
CSO

James Witter
10/15/03 04:45:41 PM
MEDICAL OFFICER
Concur

Lee Simon
10/15/03 04:55:55 PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 30, 2003
TIME: 10:00
LOCATION: S300
APPLICATION: IND# 58,362 (Acetaminophen Injection)
TYPE OF MEETING: Guidance, Type B meeting

MEETING CHAIR: Christina Fang, M.D.
MEETING RECORDER: Nancy M. Halonen

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	FDA/DAAOOP/HFD-550
Lawrence Goldkind, M.D.	Deputy Director	FDA/DAAOOP/HFD-550
James Witter, M.D., Ph.D.	Medical Team Leader	FDA/DAAOOP/HFD-550
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Carmen Debellas, R.Ph.	Chief Project Manager	FDA/DAAOOP/HFD-550
Nancy Halonen	Project Manager	FDA/DAAOOP/HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
Sandra Hamelsky, Ph.D., M.P.H.	Medical Director, Clinical Research	Bristol-Myers Squibb Co.
Rich Cuprys	Senior Dir., RA	Bristol-Myers Squibb Co.
Donna Coughlin	Assoc. Dir., RA	Bristol-Myers Squibb Co.
Howard Hoffman, M.D.	Exec. Med. Dir.	Bristol-Myers Squibb Co.
Laureen MacEachern, Ph.D., MPH	Med. Dir., Clin. Research	Bristol-Myers Squibb Co.
Jean Battikha	Assoc. Dir., Biostatistics and Data Mgt.	Bristol-Myers Squibb Co.

(b) (4)

Manuela Le Bars, M.D., Ph.D.	Assoc. Director, Pain	BMS Europe
Fanny Provot, M.D.	Manager, RA	BMS Europe

(b) (4)

Background

The sponsor has had previous meetings with the Agency to discuss NDA filing strategies and guidance in clinical development of Acetaminophen Injectable.

MEETING OBJECTIVES:

- Agency concurrence on registration strategy to support preclinical and clinical safety, and clinical pharmacology by bridging to proprietary data from EU trials dossier and available public domain data.
- Obtain guidance on proposed clinical development plans and confirm the regulatory requirements that would be the basis for an NDA filing.
- Obtain guidance on the clinical program requirements to obtain an indication of pain and fever in children, and fever in adults.

Discussion Points:

The Sponsor was provided the draft responses at the meeting. Additional commentary was generated during the discussion.

Preclinical

1. Acetaminophen has been extensively studied in animals and the results of preclinical studies support the safety for human use. No data gaps were identified that would suggest the need for additional preclinical studies at this time. To support NDA registration requirements, proprietary preclinical data for Acetaminophen Injection and references to available public domain data for acetaminophen will be provided in the NDA.

Does the Agency concur that no additional preclinical studies are required to support the NDA approval of Acetaminophen Injection? If the Agency does not agree, BMS requests guidance on this matter.

FDA Response:

- *Please provide updated information on the reproductive and genetic toxicity and carcinogenicity. If information is not available, non-clinical studies may be needed.*

Pharmacokinetics

2. Pharmacokinetic studies show that the profiles of oral acetaminophen and Acetaminophen Injection are similar. The C_{max} is higher after intravenous administration (30 µg/mL) compared to oral (20 µg/mL), and the T_{max} occurs sooner (immediately vs. 30-60 min after ingestion), but the distribution, metabolism and elimination kinetics are essentially identical. The acetaminophen pharmacokinetic profile has also been shown to be similar between Acetaminophen Injection and Propacetamol Injection. In addition, acetaminophen pharmacokinetics has also been well-characterized in special populations (e.g., renal and hepatic impaired, elderly and pediatric populations). Therefore, it is reasonable to use the existing, extensive pharmacokinetic and clinical pharmacology data from both oral acetaminophen and Propacetamol Injection to support the pharmacokinetics and clinical pharmacology for Acetaminophen Injection. In addition, a pharmacokinetic trial will be conducted to specifically characterize the pharmacokinetic profile of this formulation of Acetaminophen Injection.

Does the Agency concur that the existing body of scientific literature and clinical experience for oral acetaminophen, Propacetamol Injection, and intravenous acetaminophen, as well as the proposed pharmacokinetic trial of Acetaminophen Injection, may be used to support pharmacokinetics and clinical pharmacology labeling for Acetaminophen Injection? Does the Agency concur that no additional pharmacokinetic studies need to be conducted to support the NDA approval of Acetaminophen Injection? If the Agency does not agree, BMS requests guidance on this matter.

FDA Response:

- *No, the Agency does not concur. This is because the proposed pharmacokinetic study comparing the oral and injectable acetaminophen formulations to specifically characterize the pharmacokinetic profile of this formulation of Acetaminophen injection obtained from healthy volunteers will only allow cross-reference to the existing data on the oral formulation of acetaminophen. However, it does not address the concerns about the safety and efficacy of Acetaminophen to be used in hospitalized patients who cannot take or tolerate oral medications, and may be at increased risk for APAP associated hepatotoxicity due to an increase in exposure. Therefore PK, efficacy, and safety data need to be provided for the target population.*

Dose Response

3. Previous agreements with the Agency (12/11/96 Meeting Minutes, Propacetamol Injection – IND 51,315) indicated that the 1 g unit dose and the 4 g maximum daily dose of acetaminophen were appropriate for clinical investigation and approval. Dose response relationship of acetaminophen has been reviewed. In post-surgical pain models, the 1 g dose was statistically superior to the 0.5 g dose in providing pain relief; there was no difference between the 1 g and the 2 g doses.

Does the Agency confirm the prior agreement that the 1 g unit dose and the 4 g maximum daily dose are appropriate for Acetaminophen Injection and that no further dose response studies are necessary for NDA approval? If the Agency does not agree, BMS requests guidance on this matter.

FDA Response:

- *Single-dose studies in the dental pain and post-orthopedic surgical pain models suggested an analgesic duration of 2 to 3 hours based on median time to remedication. In the overall development for any analgesic in an acute pain setting, the Sponsor needs to adequately study and support with robust clinical trial data the “ABCs” of acute pain. In particular, this means the onset, peak effect and duration of the first, single dose (A), the dose and dosing interval for the first day (B) and the dose and dosing interval for multiple dosing beyond day one (C). The current single dose data do not support the dosing interval proposed of every 6 hours suggesting further study is necessary. A dosing interval for a product anticipated to be required for 24-48 around the clock must be safe. This is not the case for 6-8 grams per day in a postoperative patient.*
- *The quantity of rescue morphine in the orthopedic clinical study (38-mg/24 hour period 1-2 mg/hr) suggests that there is no role as monotherapy post-op. The use of 2-3 mg/hr of morphine in the placebo group suggests “opiod sparing” at best. How would this drug be labeled for post-operative analgesia?*

- *Concern regarding the burden of serious hepatotoxicity in association with the use of acetaminophen has increased in response to post-marketing reports of acute liver failure and published literature over the past several years. Dosing instructions must provide for the safe and effective use of this product in the intended population.*
- *Please provide an analysis of the post-marketing experience with parenteral acetaminophen with hepatotoxicity in greater depth than the tabulation of number of reports and include usage data. Please provide copies of any communication with regulatory agencies in countries where this product is in use regarding safety of this product.*

Clinical Program

4. Previous agreements with the Agency (12/11/96 Meeting Minutes, Propacetamol Injection – IND 51,315) indicated that two replicate studies in oral surgery pain and orthopedic surgery pain would provide sufficient evidence of efficacy for registration. Currently, BMS has conducted two randomized, placebo and active controlled Acetaminophen Injection trials in adults: single dose oral surgery pain and multiple dose orthopedic surgery pain. ^{(b) (4)}

Does the Agency confirm that the proposed Acetaminophen Injection development plan would provide sufficient evidence of efficacy for approval for the treatment of post-surgical pain in adults? If the Agency does not agree, BMS requests guidance on this matter.

FDA Response:

- *Over the past 5-6 years since discussion of efficacy endpoints for IND 51315 (Propacetamol) there have been extensive scientific discussions regarding the metrics used to assess analgesic efficacy.*
- *The current single dose data do not support the dosing interval proposed of every 6 hours.*
- *If the issue of dose duration and role of acetaminophen in the post-operative setting can be adequately addressed, the Division can give guidance on studies to achieve the information described above.*
- *Replicative evidence of efficacy in two settings of post-operative pain where a parenteral product would find use is requested to allow generalizability. Dental pain is not such a setting.*

5. The standard measures for pain intensity and pain relief will be collected. Does the Agency agree with the following primary endpoint measures?
- a) SPID 4 is the primary efficacy measure for the single dose dental surgery study and for the first dose segment of the multiple dose hip surgery study. SPID 4 is also the endpoint on which sample size is determined.
 - b) Patient global evaluation at the end of each day is the primary efficacy measure for the multiple dose study.
 - c) Rescue medication use is a secondary measure of efficacy.

FDA Response:

- (a) *In measuring single-dose effect, total pain scores in general are not considered acceptable as a primary efficacy parameter because of the potential bias introduced by differential dropout rates and inaccurate representation of time-response curves.*
- (b) *For the short-term, multiple-dose studies the primary efficacy parameter(s) should be chosen based on the question to be answered (e.g., daily average, maximum/minimum post dose, certain hours with respect to dosing time, etc.).*

The patient global at the end of the day is not adequate as a stand-alone primary efficacy measure. For short-term multiple-dose studies as is the case in acute pain, the primary efficacy parameters need to establish the analgesic characteristics that support the proposed labeling. The purpose is to study different dosing regimens and durability effect of the proposed dosage when the drug is dosed repeatedly in an in-and out-patient setting.

- (c) *How to use rescue data depends on whether patients taking rescue would be treated as treatment failure. If the data after taking rescue are to be used, rescue data need to be incorporated into pain data analysis.*

Generally speaking, use of rescue medication is considered a treatment failure of the analgesic under study. Therefore, it may be difficult to incorporate the amount of rescue into the protocol as an endpoint.

6. The proposed clinical trials will examine Patient Controlled Analgesia (PCA) requirements of active vs. control groups to evaluate the morphine sparing effect. Can this information be included in the Indication or Clinical Pharmacology sections of the labeling? Does the Agency consider the morphine sparing effect as a surrogate marker of multiple-dose efficacy?

FDA Response:

- *Morphine-sparing in an acute pain setting is problematic but may be considered supportive; it has not been used as a surrogate marker of multiple-dose efficacy. The findings from the clinical studies may be reflected in the labeling depending on the overall data. If this is the only proven potential role for therapy in post-operative settings, this previously unlabeled indication will need to be discussed.*
7. Morphine Injection is the proposed active control for our new clinical trials. Is this acceptable to the Agency? If not, what other active controls should be considered for intravenous use?

Note: Ketorolac, which is approved for post-operative use, has been removed from many hospital formularies for post-operative use, and many IRBs are reluctant to approve its use in post-operative pain trials.

FDA Response:

- *It is considered acceptable to use morphine injection as an active control in the placebo-controlled studies.*
- *The Division reminds the Sponsor that they cannot under dose morphine to produce a "morphine equivalent" database for advertising.*

8. Multiple dose experience through 48 hours will be obtained in the proposed orthopedic trial. Acetaminophen Injection will be initiated approximately 24 hours post-surgery and continued for 48 hours. Under current US hospital practice, post-operative patients are usually discharged at that time. Is 48 hour data sufficient to fulfill multiple-dose requirements for the Agency? Based on experience in controlled clinical trials up to 48 hours as well as the extensive database with long-term oral acetaminophen use

(b) (4)

FDA Response:

- *The level and duration of exposure should support the proposed dosage and time interval for actual use because of the safety concerns over the marked increase in C_{max} of the injection vs. oral formulations of acetaminophen. Consideration needs to be given to the use of daily diaries and scheduled follow-up visits to help establish the overall safety profile of this injectable formulation beyond the currently proposed 48 hour limit.*

- *The Division also recommends considering the switch to oral Acetaminophen after 48 hours.*

Safety

9. Based on similar metabolic, distribution, and elimination profiles for oral and intravenous acetaminophen, BMS believes it is reasonable to utilize the existing scientific and clinical database for oral acetaminophen and Propacetamol Injection to support the safety of Acetaminophen Injection.

The proposed Acetaminophen Injection NDA safety data will be based on:

- Acetaminophen Injection
 - 347 patients in controlled clinical trials (219 completed, 128 proposed)
 - Post-marketing exposure on (b) (4) units sold since European approval in 2001
- Propacetamol Injection experience
 - ~1500 patients in controlled clinical trials
 - Post-marketing exposure on (b) (4) units sold since European approval in 1984
- Acetaminophen oral safety experience

Does the Agency concur that the available and proposed human safety database is adequate to support safety exposure requirements for the registration of Acetaminophen Injection? Does the Agency have any additional guidance?

FDA Response:

- *The issue of safety of acetaminophen is complex, especially regarding the burden of serious hepatotoxicity as evidenced by increasing cases in post-marketing reports and the published literature. The safety of an intravenous formulation of any drug expects that a different target patient population will be exposed to this formulation vs. the same drug given orally. It may be necessary to provide PK and clinical safety data from a population of patients with prolonged or complicated illness as this product may be used in such a setting. Otherwise contraindications in all but simple post-op settings 24 hours after surgery may be needed, which currently seems unreasonable. Therefore, there needs to be a robust demonstration in the overall development program that the dose and dosing intervals proposed do not result in a significant safety liability. Safety data on the use of acetaminophen injection at the maximum recommended dosage needs to be obtained from at least 300 patients for an extended period of time. Safety data from the other formulations (oral and propacetamol) are considered supportive. In depth analysis of drug related adverse effects in the European experience would help guide this discussion.*
- *The PK and clinical effects of fasting, and hemodynamic instability that are common in hospital settings will also need to be further discussed.*

Pediatrics

10. [REDACTED] (b) (4)

BMS is requesting Agency guidance on the clinical program requirements necessary to obtain approval for the treatment of post-operative pain [REDACTED] (b) (4)

[REDACTED] (b) (4)

FDA Response:

- *This issue will need to be discussed [REDACTED] (b) (4) and should be deferred for a meeting after such consultation has taken place. Presentation of more detailed post-marketing information regarding parenteral paracetamol and acetaminophen [REDACTED] (b) (4) will be needed before such consultation can take place.*
- *This product might work well in a specialized population such as children with neutropenia and low platelet counts, or other unique small populations such as patients that cannot tolerate NSAIDs or opioids. The Sponsor is encouraged to submit information to support the scientific rationale for studying acetaminophen injection in any of these indications.*

11. Previous agreements with the Agency (12/11/96 Meeting Minutes, Propacetamol Injection – IND 51,315) indicated that one positive pediatric fever study would support a fever indication in both children and adults.

Does the Agency confirm this agreement for Acetaminophen Injection? If the Agency does not agree, BMS requests guidance on this matter.

FDA Response:

- *Please see the answer to question number 10.*

Post meeting addendum:

The proposed indication for IV acetaminophen is the treatment of post-surgical pain. This means that it would mainly be utilized in a hospital-or same day surgical-type setting. Therefore, there is a need to study acetaminophen IV in robust post-surgical pain models beyond the dental pain model. It is important to remember that patients in a post-operative setting are different than when they are exposed to this same drug given orally when they are otherwise essentially well. Consequently, major issues relate to the efficacy of acetaminophen (a relatively mild analgesic) to treat more

severe pain as being used alone and the safety issues associated with a high C_{max} (in comparison to the oral formulation of acetaminophen) with the IV injection. In fact, the duration of a single-dose effect of 1 gram of acetaminophen IV, as shown in both the dental and non-dental post-surgical studies, was only half (2-3 hours) which is very different from the proposed dosing interval (4-6 hours) which reinforces the major concern with hepatotoxicity with this compound.

The multiple-dose study of acetaminophen IV for post-surgical pain is complicated by the need for concomitant and/or rescue medication. The Division does not consider a morphine-sparing effect as a potential indication at the present time because of the difficulty in interpreting the amount of morphine spared as a clinically meaningful outcome. An exception may be if it can be demonstrated in a robust clinical manner that the reduction of morphine with the concomitant use of acetaminophen is associated with improved efficacy.

Decisions (Agreements) Reached:

The Sponsor will submit a new development program incorporating the Division's recommendations.

The Agency will need to see the European safety data to give more definitive guidance. The Agency will need to be informed about PK data and toxicity.

The Sponsor and the Agency need to further discuss the design of multi-dose studies.

The Sponsor plans to answer the safety concerns raised by the Division.

The Agency is amenable to teleconferences to give the Sponsor guidance and encourages continued dialogue to work together towards appropriate clinical protocol development.

Minutes Preparer: Nancy Halonen, Project Manager

Chair Concurrence: Christina Fang, M.D.

cc: Original
HFD-550 Div. Files
HFD550/Meeting Minutes files
HFD-550/RPM
HFD-550/Reviewers & Attendees

Drafted by: nh,
Initialed by: cf 5-10-03, jw 5-17-03
final: jw 5-23-03
MEETING MINUTES

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/s/

Lee Simon

5/28/03 05:02:17 PM



**Food and Drug Administration
Division of Anti-Inflammatory,
Analgesics and Ophthalmic Drug
Products, HFD-550**

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Number of Pages (Including Cover Page) 7

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Additional Message:
Re: IND 51,315

(b) (4)

Here are the 9-20-00 minutes. I apologize that they have been so late. We have been very short staff for a long time but that is soon to change.

Sharon A. Schmidt
Project Manager

MEETING MINUTES

MEETING DATE: 9-20-00

Time: 1:00

Location: N 225

Meeting Request Submission Date: 6-30-00

IND 51,315

Date Sponsor requested: middle Sept

IND 58,362

Briefing Document Submission Date 9-23-00

Date Meeting Scheduled: 7-12-00

Rescheduled: 8-31-00

DRUG: Propacetamol HCl/injectable acetaminophen

SPONSOR: Laboratories UPSA (Bristol-Myers Squibb Company): Quintiles, US agent

TYPE OF MEETING: (Type B) PreNDA/ End of Phase II

FDA PARTICIPANTS:

Jonca Bull - Deputy Director, ODE 5; Acting Director DAAODP, HFD-550

Robert Delap - Director ODE IV

Christina Fang – Medical Officer

Robert Osterberg – Pharm./Tox Team Leader

Asoke Mukherjee - Pharmacology Reviewer

Mona Zarifa – Chemistry Team Leader (premeeting only)

Roa Puttagunta – Chemistry Reviewer (premeeting only)

Sue-Chih Lee – Biopharm Reviewer

Abi Adebawale – Biopharm Reviewer

Leslie Vaccari – Supervisor, CSO (premeeting only)

Sharon Schmidt, Project Manager

INDUSTRY PARTICIPANTS :

Odil Hiesse-Provist, MD – Medical Advisory, Development, Laboratories UPA

Fanny Pruvot, MD Regulatory Affairs Manager, Development, Laboratories UPA

Pierre-Andre Poly, PhD– Pharmaceutical Development Director, Laboratories UPA

Jorge Insuasty, MD – Group Director Neurosciences, Clinical Research and Development, Bristol-Myers Squibb Company

(b) (4)

Anthony Abruzzini- Executive Director, Quintiles Regulatory and Technical Services

Carrie Senter – Senior Regulatory Scientist, Quintiles Regulatory and Technical Services.

MEETING OBJECTIVE:

Discuss the NDA filing strategy and questions related to filing.

SPONSOR QUESTIONS AND DISCUSSION:

1. Does the FDA agree with submitting this NDA as a 505(b)(2)?

The sponsor was asked to explain their reasoning for this approach. They stated they may want to market both products in the U.S. and wanted to reference the other drug.

The FDA stated that a 505(b)(2) is usually used when you do not have the right of reference to the data. In the case where the sponsor has the right to reference another NDA the application should reference what part of the other NDA is referenced. More discussion may be needed as their decision processes move forward.

2. The 1979 acute tox. studies were not done according to GLP. However, chronic toxicity studies (5 wks rats/5 wks monkeys) were conduct according to GLP. Is this acceptable?

The FDA stated that acute safety studies do not have to be repeated according to GLP. The existing data will be used for writing the package insert.

The pharmacology reviewer expressed safety concerns for (b) (4) on the basis of the convulsions observed in the animal acute toxicity studies. The sponsor stated that this metabolite is inert but the FDA is concerned that it may blur the safety profile as the adverse events may be due to this metabolite also.

(b) (4)

4. Does the FDA agree with the approach to the analysis of the drug-drug interaction of propacetamol to halothane?

FDA did not agree that an in vitro study is sufficient. An in vivo study with a Halothane like drug is required since literature data indicate that in mice interaction between acetaminophen and halothane varies with the timing of drug administration. The study should also reflect conditions of use, e.g., induction and/or maintenance of anesthetic.

In addition, interactions with other drugs that are likely to be given concomitantly need to be addressed. The sponsor should do further studies as necessary. If after review more pharm/tox issues arise, there may need to be some Phase 4 commitments.

5. Does the FDA agree that the same warnings and contra-indication should apply for alcoholic patients?

The sponsor should analyze data available to address the issue of potential liver toxicity of propacetamol (its Cmax is anticipated to be higher than that of oral acetaminophen) in subjects with impaired liver function and/or history of alcohol abuse. Whether such an analysis will adequately address this concern is a review issue.

The sponsor stated that patients with an alcohol abuse history were excluded from the studies conducted prior to 1997. The FDA requested the sponsor obtain the information from postmarketing surveillance data bases.

The label for these drugs should contain alcohol warnings similar to the OTC Tylenol products.

6. Does the FDA agree with including only the pivotal clinical studies in the ISE? (Page 4)

The FDA stated that a pivotal study is defined as a randomized, double blind and placebo-controlled study. If the study has only an active control and no placebo control it is not considered a pivotal study.

All the randomized, double blind and placebo-controlled studies should have a complete study report. The other studies may be presented briefly (1 page) in terms of the study design, sample population, treatments, drug exposure, major efficacy and safety findings. A summary table containing the following items would be helpful:

- 1) study identifier and the name of the principle investigator
- 2) study design (including the number of study sites)
- 3) treatments (formulation, dosage, and duration)
- 4) sample size, gender and mean age of the treatment groups
- 5) major findings summarized in a few sentences

7. Is it acceptable to include only information from the pivotal clinical studies and all spontaneous ADEs in the ISS?

The FDA requested that all safety data on propacetamol should be presented, i.e. safety data collected from clinical trials, from literature, from post-marketing surveillance (foreign countries and WHO). Safety data from different sources should be summarized in a similar fashion, as much as possible. Information on drug exposure should be summarized (e.g., dose level, number of doses, duration). There should be an attempt to analyze adverse events for their relationship to drug exposure.

In general, ICH guidelines should be followed in terms of the extent of drug exposure: a total exposure of 1500 subjects, 24-hour exposure in at least 300 subjects, and exposure in the proposed duration of use in at least 100 subjects.

The sponsor stated that data on 5-day and 14-day exposures were available and the expected duration of use is probably not going to be beyond 48 hours.

8. Does the FDA agree with performing additional analyses on the pivotal efficacy and safety studies that were not analyzed according to FDA guidelines?

Presentation on analgesic efficacy should include 5-parameter summaries (pain relief, pain intensity difference, PRID, onset, and duration).

The sponsor stated that of the 15 so called pivotal studies, 10 were analyzed according to the FDA's Guideline for Presentation of Efficacy Results. They agreed to present as much as possible according to the 5 parameters following the presentation format, for all 15 pivotal studies.

9. Would the FDA consider a waiver of the requirement for Case Report Form tabulations?

For the randomized, double blind, and placebo-controlled studies, data listings containing basic data collected through case report forms (CRFs) should be submitted. The CRFs for the cases of deaths and early terminations should also be submitted. All the CRFs from these studies should be available if needed later.

Per subject CRF tabulation is not considered very useful.

10. Does the FDA agree with the audit of 3/11 PK and 6/14 efficacy and/or safety studies? (Page 4)

The FDA is revising their answer to question #10 in their September 20,2000, minutes to read: FDA requested the sponsor to submit all the adequately designed and well controlled (randomized, double blind and placebo-controlled) studies that provide substantial evidence to support efficacy.

11. Does the FDA agree with what is required for financial disclosure?

For information on how to meet financial disclosure requirements in an NDA, please contact Linda Carter for specific advise at 301-594-6758.

12. FDA noted that there were no chemistry questions in the meeting package, but we offer that the chemistry reviewers are available for a separate meeting/telecon.

Although, there were no chemist in attendance, FDA noted that the drug appears to become unstable after a few hours of having been reconstituted. The sponsor stated that data is now available to demonstrate stability to 2 hours.

13. We note there were no questions regarding the IND 58,362.

The sponsor was encouraged to submit any questions they may have for the FDA on their IND 58,362 at a latter date.

_____	Concurrence Chair: _____
Sharon Schmidt	Jonica Bull, MD
Project Manager	Deputy ODE V Director
	Acting Dir. DAAODP

**CC: IND 51,315
IND 51,362**

MEETING MINUTES

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/s/

Sharon Schmidt
9/5/01 03:13:47 PM
CSO