

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-348**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22-348

SUPPL #

HFD # 170

Trade Name Caldolor

Generic Name Ibuprofen Injection

Applicant Name Cumberland Pharmaceuticals

Approval Date, If Known 6/11/09

### 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#

Ibuprofen

NDA# 20-716 Vicoprofen

NDA# 21-903 Neoprofen

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Investigation #1: Study CPI-CL-004  
Investigation #2: Study CPI-CL-006  
Investigation #3: Study CPI-CL-008b

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

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

investigations listed in 2C

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

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

Investigation #1 !  
!  
IND # 62,605 YES  ! NO   
! Explain:

Investigation #2 !  
!  
IND # 62,605 YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES  ! NO

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

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

YES

NO

If yes, explain:

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Name of person completing form: Ellen Fields, MD

Title: Clinical Team Leader

Date: June 8, 2009

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

Title: Deputy Division Director, DAARP

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

## Addendum to Exclusivity Form

### Additional approved Ibuprofen products

| Proprietary Name               | Active Ingredient  | Strength  | NDA#          | Approval date |
|--------------------------------|--|---|---------------|---------------|
| Rx                             |  |   |               |               |
| Neoprofen                      | Ibuprofen lysine   | EQ 20mg base/2mL (EQ 10mg base/mL)                  | <u>021903</u> | Apr 13, 2006  |
| Combunox                       | Ibuprofen; oxycodone hydrochloride                                 | 400mg;5mg   | <u>021378</u> | Nov 26, 2004  |
| Vicoprofen                     | Hydrocodone bitartrate; ibuprofen                                  | 7.5mg;200mg   | <u>020716</u> | Sep 23, 1997  |
| Generic                        | Ibuprofen suspension   | 100mg/5mL   | Multiple      |               |
| Generic                        | Ibuprofen tablet   | 400mg, 600mg, 800mg                                 | Multiple      |               |
| OTC                            |  |   |               |               |
| Advil PM                       | Diphenhydramine citrate; ibuprofen                                 | 38mg;200mg  | <u>021394</u> | Dec 21, 2005  |
| Advil PM                       | Diphenhydramine hydrochloride; ibuprofen capsule                   | 25mg;EQ 200mg free acid and potassium salt          | <u>021393</u> | Dec 21, 2005  |
| Children's Advil Allergy Sinus | Chlorpheniramine maleate; ibuprofen; pseudoephedrine hydrochloride | 1mg/5mL; 100mg/5mL; 15mg/5mL                        | <u>021587</u> | Feb 24, 2004  |
| Advil Allergy Sinus            | Chlorpheniramine maleate; ibuprofen; pseudoephedrine hydrochloride | 2mg;200mg;30mg                                      | <u>021441</u> | Dec 19, 2002  |
| Advil Cold and Sinus           | Ibuprofen; pseudoephedrine hydrochloride                           | EQ 200mg free acid and potassium salt; 30mg capsule | <u>021374</u> | May 30, 2002  |
| Children's Advil Cold          | Ibuprofen; pseudoephedrine hydrochloride                           | 100mg/5mL;15mg/5mL suspension                       | <u>021373</u> | Apr 18, 2002  |
| Children's Motrin Cold         | Ibuprofen; pseudoephedrine hydrochloride                           | 100mg/5ml;15mg/5mL suspension                       | <u>021128</u> | Aug 1, 2000   |
| Sine-Aid IB                    | Ibuprofen; pseudoephedrine hydrochloride                           | 200mg;30mg tablet                                   | <u>019899</u> | Dec 31, 1992  |
| Advil Cold and Sinus           | Ibuprofen; pseudoephedrine   | 200mg;30mg tablet                                   | <u>019771</u> | Sep 19, 1989  |

|  |                            |                                       |               |                 |
|--|----------------------------|---------------------------------------|---------------|-----------------|
|  | hydrochloride              |                                       |               |                 |
| Children's Elixsure                          | Ibuprofen suspension       | 100mg/5mL                             | <u>021604</u> | Jan 7, 2004     |
| Children's Advil                             | Ibuprofen suspension       | 100mg/5mL                             | <u>020589</u> | Jun 27,<br>1996 |
| Children's Motrin                            | Ibuprofen suspension       | 100mg/5mL                             | <u>020516</u> | Jun 16,<br>1995 |
| Midol Liquid Gels                            | Ibuprofen capsule          | Capsule 200MG                         | <u>021472</u> | Oct 18,<br>2002 |
| Advil Migraine Liqui-Gels & Advil Liqui-Gels | Ibuprofen capsule          | EQ 200mg free acid and potassium salt | <u>020402</u> | Apr 20,<br>1995 |
| Children's & Junior Strength Advil           | Ibuprofen chewable tablet  | 50mg, 100mg                           | <u>020944</u> | Dec 18,<br>1998 |
| Children's & Junior Strength Motrin          | Ibuprofen chewable tablet  | 50mg, 100mg                           | <u>020601</u> | Nov 15,<br>1996 |
| Pediatric Advil                              | Ibuprofen suspension/drops | 100mg/2.5mL                           | <u>020812</u> | Jan 30,<br>1998 |
| Children's Motrin                            | Ibuprofen suspension/drops | 40mg/mL                               | <u>020603</u> | Jun 10,<br>1996 |
| Junior Strength Advil                        | Ibuprofen tablet           | 100mg                                 | <u>020267</u> | Dec 13,<br>1996 |
| Junior Strength Motrin                       | Ibuprofen tablet           | 100mg                                 | <u>020602</u> | Jun 10,<br>1996 |
| Motrin Migraine Pain                         | Ibuprofen tablet           | 200mg                                 | <u>019012</u> | Dec 17,<br>1990 |
| Advil  | Ibuprofen tablet           | 200mg                                 | <u>018989</u> | May 18,<br>1984 |

Investigation 3 was carried out under IND and was not relied upon by the Agency to demonstrate the effectiveness of a previously approved drug.

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

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Sharon Hertz  
6/11/2009 02:45:52 PM

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

NDA/BLA#: 22-348 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DAARP PDUFA Goal Date: 6/11/09 Stamp Date: 12/11/2008

Proprietary Name: \_\_\_\_\_

Established/Generic Name: Ibuprofen

Dosage Form: Injection

Applicant/Sponsor: Cumberland Pharmaceuticals

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

- (1) \_\_\_\_\_  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_

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

Number of indications for this pending application(s): 2  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Treatment of fever

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

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

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

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

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

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

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

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

**Q3:** Does this indication have orphan designation?

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

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

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

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

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

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

Justification attached.

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

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

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

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

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

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

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

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

# Not feasible:

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

\* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

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

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

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

| Deferrals (for each or all age groups):                       |               |               |                                     | Reason for Deferral          |   |   | Applicant Certification † |
|---|---------------|---------------|-------------------------------------|------------------------------|---|---|---------------------------|
|   |               |               |                                     | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received                  |
| Population  | minimum       | maximum       |                                     |                              |   |   |                           |
| <input type="checkbox"/> Neonate                              | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  |                           |
| <input type="checkbox"/> Other                                | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  |                           |
| <input type="checkbox"/> Other                                | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  |                           |
| <input type="checkbox"/> Other                                | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  |                           |
| <input type="checkbox"/> Other                                | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  |                           |
| <input checked="" type="checkbox"/> All Pediatric Populations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input checked="" type="checkbox"/> | <input type="checkbox"/>     | <input type="checkbox"/>                      | <input type="checkbox"/>                  |                           |
| Date studies are due (mm/dd/yy): <u>01/01/11</u>              |               |               |                                     |                              |   |   |                           |

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

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

\* Other Reason: \_\_\_\_\_

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

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

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

| Pediatric subpopulation(s) in which studies have been completed (check below): |                              |               |               |   |                             |
|--|------------------------------|---------------|---------------|---|-----------------------------|
| Population   |                              | minimum       | maximum       | PeRC Pediatric Assessment form attached?. |                             |
| <input type="checkbox"/>   | Neonate                      | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |

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

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

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

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

| Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed: |                              |               |               |  |  |
|--|------------------------------|---------------|---------------|--|--|
| Population   |                              | minimum       | maximum       |  |  |
| <input type="checkbox"/>   | Neonate                      | __ wk. __ mo. | __ wk. __ mo. |  |  |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |  |  |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |  |  |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |  |  |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |  |  |
| <input type="checkbox"/>   | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. |  |  |

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

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

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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

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

| Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations: |                              |               |               |                          |                          |
|---|------------------------------|---------------|---------------|--------------------------|--------------------------|
| Population  |                              | minimum       | maximum       | Extrapolated from:       |                          |
|   |                              |               |               | Adult Studies?           | Other Pediatric Studies? |
| <input type="checkbox"/>  | Neonate                      | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

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

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

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

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

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

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

**Attachment A**

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

**Indication #2: Management of pain****Q1:** Does this indication have orphan designation?

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

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

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

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

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

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

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

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

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

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

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

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

**#** Not feasible:

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

**\*** Not meaningful therapeutic benefit:

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

**†** Ineffective or unsafe:

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

**Δ** Formulation failed:

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

Justification attached.

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

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

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

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

| Deferrals (for each or all age groups):                       |               |               |                                     | Reason for Deferral                           |   |                          | Applicant Certification † |
|---|---------------|---------------|-------------------------------------|---|---|--------------------------|---------------------------|
| Population  | minimum       | maximum       | Ready for Approval in Adults        | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received                 |                           |
| <input type="checkbox"/> Neonate                              | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/> |                           |
| <input type="checkbox"/> Other                                | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/> |                           |
| <input type="checkbox"/> Other                                | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/> |                           |
| <input type="checkbox"/> Other                                | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/> |                           |
| <input type="checkbox"/> Other                                | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/> |                           |
| <input checked="" type="checkbox"/> All Pediatric Populations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input checked="" type="checkbox"/> | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/> |                           |
| Date studies are due (mm/dd/yy): <u>01/01/12</u>              |               |               |                                     |   |   |                          |                           |

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

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

\* Other Reason: \_\_\_\_\_

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.**

**This page was completed by:**

{See appended electronic signature page}

\_\_\_\_\_  
**Regulatory Project Manager**

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

**(Revised: 6/2008)**

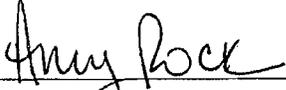
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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Kathleen Davies  
6/1/2009 03:21:08 PM

**DEBARMENT CERTIFICATION**

Cumberland 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.

 06 OCT 2008

Amy D. Rock, Ph.D.  
Senior Manager, Regulatory Affairs  
Cumberland Pharmaceuticals Inc.

## ACTION PACKAGE CHECKLIST

| <b>APPLICATION INFORMATION<sup>1</sup></b>   |                               |  |
|--|-------------------------------|--|
| NDA # 22-348<br>BLA #  | NDA Supplement #<br>BLA STN # | If NDA, Efficacy Supplement Type:  |
| Proprietary Name: Caldolor<br>Established/Proper Name: Ibuprofen Injection<br>Dosage Form: 400 mg/4mL, 800 mg/8mL  |                               | Applicant: Cumberland Pharmaceuticals<br>Agent for Applicant (if applicable):  |
| RPM: Kathleen Davies   |                               | Division: DAARP  |
| <p><b>NDA's:</b><br/>           NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)<br/>           Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> |                               | <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u><br/>           Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>NDA 20-516 Children's Motril Oral Suspension, NDA 20-402 Advil Liqui-Gels Oral Capsule, NDA 17-463 Motrin Oral Tablet</p> <p>Provide a brief explanation of how this product is different from the listed drug.<br/>           It is an injectable product.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input checked="" type="checkbox"/> No changes      <input type="checkbox"/> Updated<br/>           Date of check: 6/1/09</p> <p><b>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.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p> |
| ❖ User Fee Goal Date<br>Action Goal Date (if different)  |                               | June 11, 2009  |
| ❖ Actions  |                               |  |
| • Proposed action  |                               | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE<br><input type="checkbox"/> NA <input type="checkbox"/> CR  |
| • Previous actions ( <i>specify type and date for each action taken</i> )  |                               | <input checked="" type="checkbox"/> None   |
| ❖ Advertising ( <i>approvals only</i> )<br>Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed ( <i>indicate dates of reviews</i> )   |                               | <input checked="" type="checkbox"/> Requested in AP letter<br><input type="checkbox"/> Received and reviewed   |

<sup>1</sup> 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 <sup>2</sup> Characteristics  |   |
| Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority<br>Chemical classification (new NDAs only):<br><br><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch<br><input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch<br><input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC<br><br>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)<br><input type="checkbox"/> Restricted distribution (21 CFR 314.520)<br>Subpart I <input type="checkbox"/> Approval based on animal studies<br><br><input type="checkbox"/> Submitted in response to a PMR<br><input type="checkbox"/> Submitted in response to a PMC<br><br>Comments: |   |
| ❖ Application Integrity Policy (AIP) <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">http://www.fda.gov/ora/compliance_ref/aip_page.html</a>  |   |
| • Applicant is on the AIP   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • This application is on the AIP  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • If yes, exception for review granted ( <i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i> )   | <input type="checkbox"/> Yes  |
| • If yes, OC clearance for approval ( <i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i> )  | <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action  |
| ❖ Date reviewed by PeRC ( <i>required for approvals only</i> )<br>If PeRC review not necessary, explain: <input type="checkbox"/>   | 5/13/09   |
| ❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )  | <input type="checkbox"/> Yes, date  |
| ❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )  | <input type="checkbox"/> Yes <input type="checkbox"/> No  |
| ❖ Public communications ( <i>approvals only</i> )   |   |
| • Office of Executive Programs (OEP) liaison has been notified of action  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • Press Office notified of action   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • Indicate what types (if any) of information dissemination are anticipated   | <input checked="" type="checkbox"/> None<br><input type="checkbox"/> HHS Press Release<br><input type="checkbox"/> FDA Talk Paper<br><input type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other |

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

|  |  |
|--|--|
| ❖ Exclusivity  |  |
| <ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes  |
| <ul style="list-style-type: none"> <li>NDA and BLA: 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></li> </ul>   | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If, yes, NDA/BLA # _____ and date exclusivity expires: _____                                  |
| <ul style="list-style-type: none"> <li>(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></li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>(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></li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>(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></li> </ul>   | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>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></li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date 10-year limitation expires: _____                                |
| ❖ Patent Information (NDAs only)   |  |
| <ul style="list-style-type: none"> <li>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.</li> </ul>  | <input checked="" type="checkbox"/> Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.   |
| <ul style="list-style-type: none"> <li>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.</li> </ul>   | 21 CFR 314.50(i)(1)(i)(A)<br><input checked="" type="checkbox"/> Verified<br><br>21 CFR 314.50(i)(1)<br><input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>   | <input checked="" type="checkbox"/> No paragraph III certification<br>Date patent will expire _____  |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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></li> </ul> | <input type="checkbox"/> N/A (no paragraph IV certification)<br><input checked="" type="checkbox"/> Verified   |

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

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

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

Yes     No

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

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

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

Yes     No

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

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

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

Yes     No

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

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

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

Yes     No

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

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

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

**CONTENTS OF ACTION PACKAGE**

|  |   |
|--|---|
| ❖ Copy of this Action Package Checklist <sup>3</sup> | X |
|--|---|

**Officer/Employee List**

|   |  |
|---|--|
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> ) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/nonconsent by officers/employees   | <input checked="" type="checkbox"/> Included |

**Action Letters**

|   |                                   |
|---|-----------------------------------|
| ❖ Copies of all action letters ( <i>including approval letter with final labeling</i> ) | Action(s) and date(s) AP, 6/11/09 |
|---|-----------------------------------|

**Labeling**

|  |   |
|--|---|
| ❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )   |   |
| ❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)   |   |
| ❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)                                     |   |
| ❖ Original applicant-proposed labeling   |   |
| ❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable  |   |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> ) | <input type="checkbox"/> Medication Guide<br><input type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input checked="" type="checkbox"/> None |
| ❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)   |   |

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

|   |   |
|---|---|
| ❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)  |   |
| ❖ Original applicant-proposed labeling  |   |
| ❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable   |   |
| ❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date at upper right of first page of each submission</i> )  |   |
| ❖ Most-recent division proposal for (only if generated after latest applicant submission)   |   |
| ❖ Most recent applicant-proposed labeling   | May 29, 2009  |
| ❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )  | <input type="checkbox"/> RPM<br><input checked="" type="checkbox"/> DMEDP 5/20/09, 3/25/09<br><input type="checkbox"/> DRISK<br><input checked="" type="checkbox"/> DDMAC 5/15/09<br><input type="checkbox"/> CSS<br><input checked="" type="checkbox"/> Other reviews TN: 5/1/09, 2/4/09 |
| <b>Administrative / Regulatory Documents</b>  |   |
| ❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )  |   |
| ❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )   | <input checked="" type="checkbox"/> Included  |
| ❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If approval action, OC clearance for approval</li> </ul>  | <input checked="" type="checkbox"/> Not on AIP  |
| ❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )   | <input checked="" type="checkbox"/> Included  |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )   | <input checked="" type="checkbox"/> Verified, statement is acceptable   |
| ❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> <li>• Outgoing communications (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submissions/communications</li> </ul>  | <input checked="" type="checkbox"/> None  |
| ❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submission documenting commitment</li> </ul>  | <input checked="" type="checkbox"/> None  |
| ❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )  | X   |
| ❖ Internal memoranda, telecons, etc.  | N/A   |
| ❖ Minutes of Meetings <ul style="list-style-type: none"> <li>• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>• Regulatory Briefing (<i>indicate date</i>)</li> <li>• Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>• EOP2 meeting (<i>indicate date</i>)</li> <li>• Other (e.g., EOP2a, CMC pilot programs)</li> </ul> | <input checked="" type="checkbox"/> Not applicable<br><input checked="" type="checkbox"/> No mtg<br><input type="checkbox"/> No mtg 5/29/08<br><input checked="" type="checkbox"/> No mtg<br>7/15/05, 4/23/04, 10/22/03   |

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.

|  |   |
|--|---|
| Advisory Committee Meeting(s)  | <input checked="" type="checkbox"/> No AC meeting |
| <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> <li>48-hour alert or minutes, if available</li> </ul>  |   |
| <b>Decisional and Summary Memos</b>  |   |
| ❖ 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                     |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None                     |
| <b>Clinical Information<sup>5</sup></b>  |   |
| ❖ Clinical Reviews   |   |
| <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>  | N/A   |
| <ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>  | 5/20/09   |
| <ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>  | <input checked="" type="checkbox"/> None          |
| ❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )  | incl in review                                    |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, review/memo explaining why not   | incl in review                                    |
| ❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )   | <input checked="" type="checkbox"/> None          |
| Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )   | <input checked="" type="checkbox"/> Not needed    |
| ❖ REMS <ul style="list-style-type: none"> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>)</li> </ul> | <input checked="" type="checkbox"/> None          |
| ❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )   | <input type="checkbox"/> None requested           |
| <ul style="list-style-type: none"> <li>Clinical Studies</li> </ul>   | 5/8/09, 5/19/09                                   |
| <ul style="list-style-type: none"> <li>Bioequivalence Studies</li> </ul>   | N/A   |
| <ul style="list-style-type: none"> <li>Clinical Pharmacology Studies</li> </ul>  | N/A   |
| <b>Clinical Microbiology</b> <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                     |
| <b>Biostatistics</b> <input type="checkbox"/> None   |   |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None          |
| Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None 5/17/09             |
| Statistical Review(s) ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None 5/8/09              |
| <b>Clinical Pharmacology</b> <input type="checkbox"/> None   |   |
| ❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None          |
| Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None          |

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

|  |  |
|--|--|
| Clinical Pharmacology review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None 5/11/09  |
| ❖ DSI Clinical Pharmacology Inspection Review Summary  | <input checked="" type="checkbox"/> None   |
| <b>Nonclinical</b> <input type="checkbox"/> None   |  |
| ❖ Pharmacology/Toxicology Discipline Reviews   |  |
| • ADP/T Review(s) <i>(indicate date for each review)</i>   | <input checked="" type="checkbox"/> None   |
| • Supervisory Review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None 5/19/09  |
| • Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>   | <input type="checkbox"/> None 5/15/09  |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>  | <input checked="" type="checkbox"/> None   |
| ❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>  | <input checked="" type="checkbox"/> No carc  |
| ❖ ECAC/CAC report/memo of meeting  | <input checked="" type="checkbox"/> None<br>Included in P/T review, page   |
| ❖ DSI Nonclinical Inspection Review Summary  | <input checked="" type="checkbox"/> None requested   |
| <b>CMC/Quality</b> <input type="checkbox"/> None   |  |
| ❖ CMC/Quality Discipline Reviews   |  |
| • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>   | <input checked="" type="checkbox"/> None   |
| • Branch Chief/TeamLeader Review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None 5/27/09  |
| • CMC/product quality review(s) <i>(indicate date for each review)</i>   | <input type="checkbox"/> None 5/22/09  |
| • BLAs only: Facility information review(s) <i>(indicate dates)</i>  | <input checked="" type="checkbox"/> None   |
| ❖ Microbiology Reviews   |  |
| • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>  | 5/11/09<br><input type="checkbox"/> Not needed   |
| • BLAs: Sterility assurance, product quality microbiology  |  |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date for each review)</i>  | <input checked="" type="checkbox"/> None   |
| ❖ Environmental Assessment (check one) (original and supplemental applications)  |  |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> |  |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>   |  |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>   |  |
| ❖ Facilities Review/Inspection   |  |
| • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>  | Date completed:<br><input type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation               |
| • BLAs:  |  |
| ➤ TBP-EER  | Date completed:<br><input type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation               |
| ➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i>                         | Date completed:<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Accepted <input type="checkbox"/> Hold |

❖ NDAs: Methods Validation

- Completed
- Requested
- Not yet requested
- Not needed

## Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

## PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

NDA: 22-348

### PMR/PMC Title:

Assessment of pharmacokinetics, safety, and efficacy of IV Ibuprofen for the management of pain in pediatric patients from birth to 16 years of age.

### PMR/PMC Schedule Milestones:

Protocol Submission: November 2010

Study Start Date: January 2011

Final Report Submission: January 2012

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Studies in adults were complete and ready for approval

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. *If not a PMR, skip to 3.*

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

No pharmacokinetic data, efficacy or safety available for the pediatric population

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?

Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

**Not applicable.**

4. If not required by regulation, characterize the review issue leading to this PMC

**Not applicable**

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

Pharmacoepidemiologic study (list risk to be evaluated)

Registry studies

Primary safety study or clinical trial (list risk to be evaluated)

Subpopulation (list type)

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing studies

- Additional data or analysis required for a previously submitted or expected study (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other (provide explanation)

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

**CDTL or PMR/PMC Development Coordinator:**

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.  
Deputy Director for Safety  
CDER/OND/ODE II/DAARP

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

-----  
Kathleen Davies  
6/12/2009 03:48:45 PM  
CSO

Ellen Fields  
6/12/2009 03:49:43 PM  
MEDICAL OFFICER

Larissa Lapteva  
6/13/2009 09:50:17 PM  
MEDICAL OFFICER

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This template should be completed by review management and included for each PMR/PMC in the Action Package.

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Larissa Lapteva, M.D., M.H.S.  
Deputy Director for Safety  
CDER/OND/ODE II/DAARP

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Kathleen Davies  
6/12/2009 03:48:45 PM  
CSO

Ellen Fields  
6/12/2009 03:49:43 PM  
MEDICAL OFFICER

Larissa Lapteva  
6/13/2009 09:50:17 PM  
MEDICAL OFFICER

**From:** [Amy D. Rock](#)  
**To:** [Davies, Kathleen](#);  
**cc:** [Leo Pavliv](#);  
**Subject:** Paragraph IV certification, FW: Follow up ibuprofen patent information  
**Date:** Monday, June 01, 2009 4:43:56 PM

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Kathleen:

Please see the emails below - I have directly forwarded the communication we received from the patent holder. Please let me know if I should submit this correspondence to the NDA.

Best regards,  
Amy

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

From: Leo Pavliv [<mailto:lpavliv@cumberlandpharma.com>]  
Sent: Monday, June 01, 2009 3:31 PM  
To: Amy D. Rock  
Subject: FW: Follow up ibuprofen patent information

Amy

Here is the correspondence with J&J senior Counsel, acknowledging receipt and destruction of the additional information provided to J&J regarding the patent.

Leo Pavliv  
Vice President Operations  
Cumberland Pharmaceuticals  
2525 West End Ave Ste 950  
Nashville TN 37203  
NC Phone 919-481-2974  
Main Phone 615-255-0068  
Fax 615-255-0094  
e-mail: [lpavliv@cumberlandpharma.com](mailto:lpavliv@cumberlandpharma.com)

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

From: Reda, Jennifer [JJCUS] [<mailto:JReda@its.jnj.com>]  
Sent: Wednesday, April 01, 2009 8:45 AM  
To: Leo Pavliv  
Subject: RE: Follow up ibuprofen patent information

Dear Mr. Pavliv:

Thank you for providing the requested information relating to Cumberland's 505(b)(2) application for an ibuprofen injectable. This is to confirm that I have deleted the electronic version of the information you sent as well as any printed hard copies.

Please let me know if you have any questions.

Regards,  
Jennifer  
Jennifer A. Reda  
Senior Counsel

Johnson & Johnson  
One Johnson & Johnson Plaza  
New Brunswick, New Jersey 08933  
Tel.: (732) 524-5320  
Fax: (732) 524-5334  
jreda@its.jnj.com

This message is intended only for the individual or entity to which it is addressed and may contain information that is PRIVILEGED, CONFIDENTIAL AND EXEMPT FROM DISCLOSURE UNDER APPLICABLE LAW. If the reader of this message is not the intended recipient, or the employee or agent responsible for delivering the message solely to the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please delete the original message immediately and notify us by telephone. Thank you.

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

From: Leo Pavliv [<mailto:lpavliv@cumberlandpharma.com>]

Sent: Tuesday, March 10, 2009 2:26 PM

To: Reda, Jennifer [JJCUS]

Subject: Follow up ibuprofen patent information

Jennifer

As promised, I've attached a partly redacted section 3.2.P.1 from our NDA that states the qualitative composition of our product. As you can see it does not infringe J&J's patent.

Could you please confirm receipt of this e-mail and also after you review, please confirm that you believe it does or does not infringe on J&J's patent? Also, I would appreciate if after reviewing the attached information, you could please delete the attachment and destroy any printed copies of it.

Please let me know if you have any questions or if I can help your evaluation in any other way.

Regards,

Leo

Leo Pavliv

Vice President Operations

Cumberland Pharmaceuticals

2525 West End Ave Ste 950

Nashville TN 37203

NC Phone [REDACTED] (b) (4)

Main Phone 615-255-0068

Fax 615-255-0094

e-mail: [lpavliv@cumberlandpharma.com](mailto:lpavliv@cumberlandpharma.com)

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

-----  
Kathleen Davies  
6/2/2009 12:02:05 PM  
CSO

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** RE: NDA 22-348 IR  
**Date:** Tuesday, May 19, 2009 2:23:30 PM

---

Hi Amy,

We have another IR for you below based upon a review received from the Division of Scientific Investigations. We request a prompt response to this request as we are getting closer to your action date.

If you have any questions, let me know.

Kathleen

*Based on concerns identified during a FDA site inspection, it is necessary that you reanalyze the data for Study CPI-CL-008B. The primary analysis should be repeated excluding data from site 2 (Dr. Lamar Snow, clinical investigator). In addition, Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.1.3 and 14.2.1.1.4 should be reproduced from the analyses excluding the site. Provide all supporting documentation including the results from the initial model as well as subsequent models such that each step in the model selection procedure is readily apparent.*

**From:** Davies, Kathleen  
**To:** Amy D. Rock;  
**Subject:** RE: NDA 22-348 IR  
**Date:** Thursday, May 14, 2009 8:51:54 PM

---

Hi Amy,

I have another question for you:

On page 41 of the Clinical Study Report for Study CPI-CL-008A, you state the following:

The primary endpoint for the study was reduction in the requirement for morphine use in the 24 hours following surgery as measured by total morphine usage compared to placebo. Analysis of variance and covariance procedures were to be used to compare the reduction in the requirement for morphine use in the 24 hours following surgery among the treatment groups. Dunnett's test was to be used as a multiple comparison test to compare active dose groups with the placebo group at an overall alpha level of 0.05. Comparison of morphine use among active doses of IVIb was to be made using an alpha level of 0.10 to declare significance. In the primary model, center was to be introduced as a covariate. Center-by-Treatment interaction was to be examined to evaluate the consistency of results among centers for the primary efficacy endpoint, morphine requirements post-surgery. Type of surgery, weight, gender and other covariates identified through the demographic, background and baseline analysis were to be introduced as secondary covariates **for sensitivity analysis and robustness.**

Based on the aforementioned, it appears that the primary model only included factors for treatment and center, and other covariates were to be introduced for sensitivity analyses and robustness. However in your NDA, the primary model appears to include factors for treatment, center, weight, and age. Explain this apparent discrepancy, and indicate where the results for the primary model are located within your NDA.

---

**From:** Amy D. Rock [mailto:arock@cumberlandpharma.com]  
**Sent:** Thu 5/14/2009 4:36 PM  
**To:** Davies, Kathleen

**Subject:** RE: NDA 22-348 IR

Kathleen-

Files are attached.

Please let me know if you need anything else or any further clarification/information.

Best,

Amy

---

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

**Sent:** Thursday, May 14, 2009 3:32 PM

**To:** Amy D. Rock

**Subject:** RE: NDA 22-348 IR

Hi Amy,

Please provide the supporting documentation via email.

Kathleen

---

**From:** Amy D. Rock [mailto:arock@cumberlandpharma.com]

**Sent:** Thursday, May 14, 2009 3:34 PM

**To:** Davies, Kathleen

**Subject:** NDA 22-348 IR

**Importance:** High

Kathleen:

Attached is the response for the statistical information request from yesterday. The formal submission is going into the eCTD via the Gateway today.

I have not attached the supporting documentation for the model approach to this email. Please let me know if you would like that via email.

Best regards,

Amy

**Amy Rock, PhD**

Senior Manager, Regulatory Affairs

Cumberland Pharmaceuticals Inc.

2525 West End Avenue, Suite 950

Nashville, TN 37203

Ph 615.255.0068

[www.cumberlandpharma.com](http://www.cumberlandpharma.com)

**From:** [Davies, Kathleen](#)  
**To:** "Amy D. Rock";  
**Subject:** RE: NDA 22-348; Follow-Up IR  
**Date:** Wednesday, May 13, 2009 2:54:51 PM  
**Attachments:** [IRIVibu.doc](#)

---

Hi Amy,

See attached clarification. Let me know if you have further questions.

Kathleen

---

**From:** Amy D. Rock [mailto:[arock@cumberlandpharma.com](mailto:arock@cumberlandpharma.com)]  
**Sent:** Wednesday, May 13, 2009 1:48 PM  
**To:** Davies, Kathleen  
**Subject:** RE: NDA 22-348; Follow-Up IR  
**Importance:** High

Kathleen:

We believe the final study report for CPI-CL-008B did follow the analyses according to the SAP dated 09 Jan 2008. This SAP was submitted to the FDA in IND amendment SN#085 and was also included in the NDA (file 16.1.9, in 022348\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-pain\5351-stud-rep-contr\cpicl008b folder). Could the statistical reviewer please provide some guidance and specify what items in the report didn't coincide with the plan so that we could provide a more specific response?

Thanks very much,  
Amy

---

**From:** Davies, Kathleen [mailto:[Kathleen.Davies@fda.hhs.gov](mailto:Kathleen.Davies@fda.hhs.gov)]  
**Sent:** Wednesday, May 13, 2009 8:39 AM  
**To:** Amy D. Rock  
**Subject:** RE: NDA 22-348; Follow-Up IR

Hi Amy,

I have a question from the statistical team. Since the review clock is winding down, I request a response by COB Thursday.

*The analyses outlined in the Final Study Report for CPL-CL-008B do not coincide with the analyses outlined in the Statistical Analysis Plan. Explain this discrepancy.*

Thanks,

Kathleen

---

**From:** Amy D. Rock [mailto:arock@cumberlandpharma.com]  
**Sent:** Tuesday, May 12, 2009 10:20 AM  
**To:** Davies, Kathleen  
**Subject:** NDA 22-348; Follow-Up IR

Kathleen:

Reference is made to NDA 22-348 and the teleconference and email correspondence dated 07-April-09 containing an information request from the Quality reviewers. Please find attached additional information to that provided on 20 April 2009 (Sequence 0014). This information is being formally submitted today/tomorrow – but I wanted you to have a copy.

I also wanted to ask if all of our previous responses for clarification were received, acceptable and if there were any questions from the reviewers?

Best regards,  
Amy

**Amy Rock, PhD**  
Senior Manager, Regulatory Affairs  
Cumberland Pharmaceuticals Inc.  
2525 West End Avenue, Suite 950  
Nashville, TN 37203  
Ph 615.255.0068  
[www.cumberlandpharma.com](http://www.cumberlandpharma.com)

**From:** [Davies, Kathleen](#)  
**To:** ["Amy D. Rock"](#);  
**Subject:** RE: NDA 22-348; Follow-Up IR  
**Date:** Wednesday, May 13, 2009 9:38:55 AM

---

Hi Amy,

I have a question from the statistical team. Since the review clock is winding down, I request a response by COB Thursday.

*The analyses outlined in the Final Study Report for CPL-CL-008B do not coincide with the analyses outlined in the Statistical Analysis Plan. Explain this discrepancy.*

Thanks,

Kathleen

---

**From:** Amy D. Rock [<mailto:arock@cumberlandpharma.com>]  
**Sent:** Tuesday, May 12, 2009 10:20 AM  
**To:** Davies, Kathleen  
**Subject:** NDA 22-348; Follow-Up IR

Kathleen:

Reference is made to NDA 22-348 and the teleconference and email correspondence dated 07-April-09 containing an information request from the Quality reviewers. Please find attached additional information to that provided on 20 April 2009 (Sequence 0014). This information is being formally submitted today/tomorrow – but I wanted you to have a copy.

I also wanted to ask if all of our previous responses for clarification were received, acceptable and if there were any questions from the reviewers?

Best regards,  
Amy

**Amy Rock, PhD**  
Senior Manager, Regulatory Affairs  
Cumberland Pharmaceuticals Inc.  
2525 West End Avenue, Suite 950  
Nashville, TN 37203  
Ph 615.255.0068

[www.cumberlandpharma.com](http://www.cumberlandpharma.com)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

NDA 22-348

**PROPRIETARY NAME REQUEST  
- ACCEPTABLE**

Cumberland Pharmaceuticals Inc.  
2525 West End Avenue  
Suite 950  
Nashville, TN 37203

Attention: Amy D. Rock, Ph.D.  
Sr. Manager, Regulatory Affairs

Dear Dr. Rock:

Please refer to your New Drug Application (NDA), dated December 3, 2008, received December 11, 2008, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Injection 400 mg/4 mL and 800 mg/8 mL.

We also refer to your February 25, 2009 correspondence, received February 26, 2009 requesting review of your proposed proprietary name, Caldolor. We have completed our review of the proposed proprietary name, Caldolor and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 3, 2008 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, 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 the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Rigoberto Roca  
5/6/2009 12:16:39 PM  
on behalf of Bob Rappaport, M.D.

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** Additional Clinical IR  
**Date:** Tuesday, April 28, 2009 10:05:34 AM

---

Hi Amy,

In addition to the IR sent yesterday, I have the additional IR:

*Please clarify how many patients in each of the age groups 60 to <65 year and ≥65 years, received 100 mg and how many received 200 mg in Study 004.*

If you have any questions, let me know.

Kathleen

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** Clinical IR  
**Date:** Monday, April 27, 2009 10:56:55 AM

---

Hi Amy,

Please refer to NDA 22-348 for Ibuprofen IV. The clinician has the following requests for information/clarification:

*In Appendix Tables 14.3.1.1 (AEs) on page 174 and Appendix Table 14.3.1.5 (AE for critically ill population) page 182 of the report for Study 004, one case of AE listed as acetabulum fracture and one case as humerus fracture were both under IVlb 100 mg. Are they the same or different patients? If they are different patients, please provide CRF for patient with acetabulum fracture. Please confirm if the randomization number for patient with humerus bone fracture is 5055?*

*According to Appendix Table 16.2.7.1 (serious AE) on pages 1243-1245 of the report for Study 004 the patient with humerus fracture was reported as in the placebo treatment group and has a critically ill status, which is confirmed by the information recorded in the CRF that the patient received mechanical ventilation.*

*Based on the description of serious events provided on page 94 of the report for Study 004 the patient with number 5055 has a non-critically ill status.*

*Please explain all these inconsistencies and clarify the actual treatment the patient with humerus fracture received.*

If you have any questions, please let me know.

Kathleen

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** RE: NDA 22-348; Ibuprofen Injection, Pediatric Plan  
**Date:** Tuesday, April 21, 2009 2:28:15 PM

---

Hi Amy,

We received your pediatric plan.

We have a clinical request for you:

Provide the number and percentage of patients in each treatment group who are in the age group of  $\geq 65$  years old, 60 to  $< 65$  years old, and  $< 60$  years old for all phase 3 clinical studies. The information could not be found in the original submission.

If you have any questions, let me know.

Kathleen

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

From: Amy D. Rock [<mailto:arock@cumberlandpharma.com>]  
Sent: Tuesday, April 14, 2009 3:04 PM  
To: Davies, Kathleen  
Subject: NDA 22-348; Ibuprofen Injection, Pediatric Plan  
Importance: High

Kathleen:

Our Pediatric Plan (NDA 22-348, ibuprofen injection) is drafted with the information per our correspondence last week. We are ready to formally submit it, but should this be part of 1.9.2 or 1.9.5 of the eCTD? Alternatively, is this general correspondence regarding pediatrics until an agreement is reached?

Thanks for any input you can provide.

Best,  
Amy

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** RE: Pediatric Plan for NDA 22348  
**Date:** Thursday, April 02, 2009 4:27:06 PM

---

Hi Amy,

At this time, the Division cannot advise you as to whether a PWR for pain would be granted or denied. If you chose to submit a PPSR for the treatment of pain, you must submit all the necessary items for review and a convincing argument as to the public health need that would be served by a written request for [REDACTED] (b) (4).

In terms of exclusivity, you would not receive two 6-months of full exclusivity; however, it is possible to receive exclusivity for the moiety, which does include the 6 months of full exclusivity for one WR and then additional pediatric exclusivity for a specific indication, but not for the full product application. In other words, you cannot stack WRs to get 6 months exclusivity over and over again.

Whether you chose to submit a PPSR [REDACTED] (b) (4), we still have to address PREA for your application for [REDACTED] (b) (4). Written Requests fall under BCPA and are distinct from PREA.

In order to satisfy PREA, you must submit a Pediatric Plan as part of the NDA. The Pediatric Plan must include studies for [REDACTED] (b) (4). Studies must include PK, safety and efficacy. The efficacy trial must be of a randomized, double blind, superiority design. Deferrals and/or waivers may be submitted with appropriate justification. In addition, a timeline must be submitted to include the following for all proposed studies:

- Date of protocol submission
- Date of initiation of study
- Date of completion of study
- Date of final study report submission

Study protocols do not need to be submitted at this point.

If you have any questions, let me know.

Kathleen

---

**From:** Amy D. Rock [mailto:arock@cumberlandpharma.com]  
**Sent:** Monday, March 30, 2009 6:05 PM  
**To:** Davies, Kathleen  
**Subject:** RE: Pediatric Plan for NDA 22348  
**Importance:** High

Kathleen:

Cumberland is considering submitting a separate request for a PWR for (b) (4). Can you confirm that Cumberland would be eligible for an additional 6 months of exclusivity for (b) (4)? We envision that the requested PK study would be applicable for (b) (4) whereas separate fever and pain efficacy studies would then be conducted (b) (4).

If so, we would submit correspondence to the NDA requesting a deferral for (b) (4) pending the PWR.

Thanks,  
Amy

---

**From:** Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]  
**Sent:** Monday, March 30, 2009 2:31 PM  
**To:** Amy D. Rock  
**Subject:** Pediatric Plan for NDA 22348

Hi Amy,

Please refer to NDA 22-348 for Ibuprofen IV and to the PWR sent to you today for (b) (4).

Your submitted NDA includes the indications of fever and for the management of pain. Under PREA, we must address all indications noted in your application.

Please advise as to your intent for [REDACTED] (b) (4) We note in the application that you request a [REDACTED] (b) (4)

If you have any questions, please let me know.

Kathleen

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

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Kathleen Davies  
6/2/2009 11:26:12 AM  
CSO

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** NDA 22348: IR from tcon + Stats IR  
**Date:** Tuesday, April 07, 2009 2:57:19 PM  
**Attachments:** 22348 Ibuprofen IV List of Deficiencies.doc

---

Hi Amy,

The comments and requests for information noted in the t-con this morning are attached as a Word document.

In addition, we have the following statistical IR:

*In the statistical analysis plan for study CPI-CL-008B, you state, "The intent-to-treat population (ITT) will include all patients who were randomized and received at least one dose of CTM." The following subjects are listed in the tabulation file EX as having receiving at least one dose of clinical trial material, but were not included in the ITT population in the BASICS file: 03-08108, 04-05163, 04-06159, 04-06160, 04-06169, 04-07153, 04-07154, 04-08165, 07-06302, 07-06307, 07-06308. Moreover, the BASICS file indicates that these subjects did not receive clinical trial material. Explain why these subjects were excluded from the ITT population, explain the apparent discrepancies between the EX and BASICS files, and provide the case report forms.*

*In study CPI-CL-008B, the following subjects are listed in the EX file but no treatment is specified: 01-07003, 02-05053, 02-05057, 03-06120, 03-08103. Clarify whether these subjects received clinical trial material, and provide their case report forms.*

It is expected to receive a response to the stats IR by the end of the week.

Attendees of the t-con:

Dr. Sharon Hertz, Deputy Division Director  
Dr. Dan Mellon, Pharmacology Toxicology Supervisor  
Dr. Ali Al Hakim, Branch Chief, Division of Pre-Marketing Assessment, Office of New Drug Quality Assessment (ONDQA)  
Dr. Martin Haber, Chemist, ONDQA  
Kathleen Davies, PM

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** RE: NDA 22-348, PREA-Pain  
**Date:** Tuesday, April 07, 2009 11:52:54 AM

---

Hi Amy,

Thank-you for your submission with teh intent to submit a (b) (4).  
However, I need the information for PREA that was included in the original email request I sent you for both fever and pain. The statement that you intend to study under a WR is not sufficient to address PREA for your pending NDA.

*In order to satisfy PREA, you must submit a Pediatric Plan as part of the NDA. The Pediatric Plan must include studies for (b) (4) for the age groups similar to the breakdown in the PWR. Studies must include PK, safety and efficacy. The efficacy trial must be of a randomized, double blind, superiority design. Deferrals and/or waivers may be submitted with appropriate justification. In addition, a timeline must be submitted to include the following for all proposed studies:*

*Date of protocol submission  
Date of initiation of study  
Date of completion of study  
Date of final study report submission*

*Study protocols do not need to be submitted at this point.*

Without this information, we cannot address PREA for your application. I need this information as soon as possible because we must present this to the Pediatric Review Committee prior to your action date.

Kathleen

---

**From:** Amy D. Rock [mailto:arock@cumberlandpharma.com]  
**Sent:** Tuesday, April 07, 2009 11:44 AM  
**To:** Davies, Kathleen  
**Subject:** NDA 22-348, PREA-Pain  
**Importance:** High

Kathleen:

Attached is the document we intend to submit to address the PREA for (b) (4) I can submit this formally today or hold it until we have the submission ready to address the comments from today's telecon (most likely next week). Which do you prefer?

Thanks,

Amy

**Amy Rock, PhD**

Senior Manager, Regulatory Affairs

Cumberland Pharmaceuticals Inc.

2525 West End Avenue, Suite 950

Nashville, TN 37203

Ph 615.255.0068

[www.cumberlandpharma.com](http://www.cumberlandpharma.com)



NDA 22-348

**DISCIPLINE REVIEW LETTER**

Cumberland Pharmaceuticals Inc.  
2525 West End Ave., Suite 950  
Nashville, TN 37203

Attention: Amy Rock, PhD  
Senior Manager, Regulatory Affairs

Dear Dr. Rock:

Please refer to your new drug application (NDA) dated December 3, 2008, received December 11, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen Injection.

We also refer to your submission dated February 25, 2009.

The Division of Medication Error Prevention and Analysis in the Office of Surveillance and Epidemiology has completed their review of the labeling section of your submission, and have identified the following deficiencies:

A. General Comment on Container Labels and Carton Labeling:

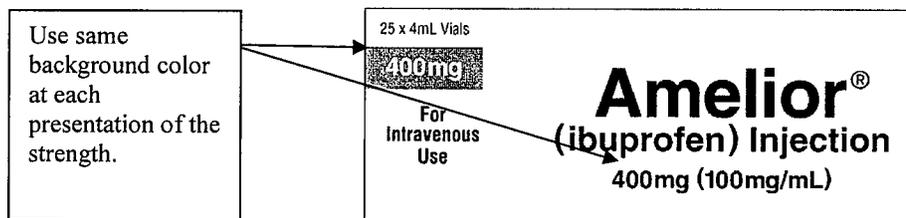
1. Revise the presentation of the strengths of the vials in terms of net quantity (i.e., 400 mg/4 mL and 800 mg/8 mL) followed by the concentration 100 mg/mL in the insert labeling, the carton labeling, and the container labels. For example:

Tradenname  
(Ibuprofen) Injection  
**400 mg/4 mL**  
(100 mg/mL)

Note the prominence of the font used for the strength compared to the concentration of the solution.

B. Carton Labeling (400 mg/4 mL and 800 mg/8 mL vials)

1. Apply the same color background blue to the strength which appears below the established name. This color block helps to distinguish the different available strengths and should be applied consistently on each label.



2. The colors contrast of [REDACTED] (b) (4) background does not provide sufficient color contrast and makes the 800 mg/8 mL strength difficult to read. Revise the colors used so that there is sufficient contrast for readability.
  3. Revise the presentation of the route of administration “FOR INTRAVENOUS USE” to appear above the storage directions on the back panel. In its current location, the statement may be overlooked.
  4. Revise the statement, “[REDACTED] (b) (4)” to read, “Single dose vial, discard unused portion.” This will ensure no remaining drug is retained for further use.
  5. Revise the presentations of the strengths and volumes by adding a space between the number and the unit of measure (i.e., 100 mg rather than 100mg).
  6. Revise the presentation of the product concentration (100 mg/mL) to appear below the vial strength. (See example provided in Comment A1.)
- C. Container Labels (400 mg/4 mL and 800 mg/8 mL vials)
1. Include the colors used to distinguish the strengths on the carton labeling.
  2. Relocate the route of administration so that it appears above the storage conditions.
  3. Revise the presentations of the strengths and volumes by adding a space between the number and the unit of measure.
  4. Revise the presentations of the strengths and volumes by adding a space between the number and the unit of measure (i.e., 100 mg rather than 100mg).
  5. Delete the net quantity volume in the upper left corner as it is redundant once you revise your statement of strength.
  6. Revise the presentation of the product concentration (100 mg/mL) to appear below the vial strength on the 800 mg/8 mL vial. (See example provided in example A1.)
- D. Insert Labeling (DOSAGE AND ADMINISTRATION Section)
1. Include the appropriate rate of infusion (e.g., infuse over 30 minutes) for prepared doses of the product in this section of the labeling.

2. Include information about the proper storage conditions (e.g., refrigeration or room temperature) and information on the stability of the product after preparation in this section of the labeling.
3. Revise preparation instructions for the 800 mg dose using the [REDACTED], whichever stability data supports.

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 Kathleen Davies, Regulatory Health Project Manager, at 301-796-2205.

Sincerely,

*{See appended electronic signature page}*

Sara Stradley, MS  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Sara Stradley  
4/2/2009 02:41:43 PM

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** NDA 22348\_Stats IR  
**Date:** Wednesday, March 18, 2009 3:40:18 PM

---

Hi Amy,

I have another Stats IR for you:

***For Studies CPI-CL-008A and CPI-CL-008B, list all subjects who received restricted analgesics (including NSAIDS) during the first 24 hours of treatment with study medication.***

I inquired with the Division of Drug Marketing about your promotional materials question; I am still waiting to hear back from them.

Kathleen

BlockFrom: Davies, Kathleen

Sent: Thursday, March 12, 2009 2:06 PM

To: 'Amy D. Rock'

Subject: NDA 22348/Ibuprofen Injection - clinical IR - IXOS CDER 130 KB

Attachments: placeholder.tmp

Hi Amy,

Please refer to NDA 22-348 for Ibuprofen IV. The clinical reviewer has the following IR (attached).

I am looking into your question regarding promotional materials and will get back to you shortly. The PWR is still under review.

Let me know if you have any additional questions.

Kathleen

## Fever studies

### 1. Study 004

#### 1) Please provide the actual number of patients used in the statistical analyses of all efficacy endpoints for ITT population

According to the protocol and Statistical Analysis Plan, ITT population in fever study 004 was defined to be all patients with a baseline assessment and at least one post baseline evaluation of the primary endpoint (temperature measurement at Hour 4 after the initial dose. According to drug exposure information 5 of the 120 treated did not get the second dose, which was given 4 hours after the initial dose. Were all 120 included in the primary analysis for the ITT population?

Similarly, there were 12 patients who did not get all 6 doses. Were they all included in the statistical analyses of the efficacy endpoints for the ITT population such as time to temperature reducing to <101.0°F (38.3°C) in 24 hours and time-specific change in temperature in 24 hours from the start of the infusion?

#### 2) Please clarify the inconsistency between 11 patients (2 on 400 mg) reported as discontinuation versus 12 patients (3 on 400 mg) reported as not receiving all 6 doses.

#### 3) Survival curves for fever reduction to temperature <100.0°F (37.8°C) in 24 hours

Please provide information on the number and percentage of patients in the ITT population who had temperature reducing to <100.0°F (37.8°C) in 24 hours and time to reach temperature <100.0°F (37.8°C) during the 24-hour period by filling in the table below and providing associated survival curves.

**Table Time to Temperature <100.0°F (37.8°C) in Hours 0-24 in ITT Population**

| Study 004  | 100 mg IVIb<br>(n=31) | 200 mg IVIb<br>(n=30) | 400 mg IVIb<br>(n=31) | Placebo<br>(n=28) |
|--|-----------------------|-----------------------|-----------------------|-------------------|
| <b>Time to T&lt;100.0°F (37.8°C) in 24 hours</b>     |                       |                       |                       |                   |
| Number (%) with T<101.0°F (38.3°C) at Hour 24        |                       |                       |                       |                   |
| Time to T<101.0°F (38.3°C) by Hour 24 (hour)*        |                       |                       |                       |                   |
| Mean (SE)  |                       |                       |                       |                   |
| Median   |                       |                       |                       |                   |
| Comparison against placebo, p-value of Log-rank test |                       |                       |                       |                   |

For your reference the table below is based on the information provided in the Appendix Table 14.2.10 on page 138 of the report for Study 004

**Table 5.3.1-9 Time to Temperature <101.0°F (38.3°C) in Hours 0-24 in ITT Population**

| Study 004  | 100 mg IVIb<br>(n=31) | 200 mg IVIb<br>(n=30) | 400 mg IVIb<br>(n=31) | Placebo<br>(n=28) |
|--|-----------------------|-----------------------|-----------------------|-------------------|
| <b>Time to T&lt;101.0°F (38.3°C) in 24 hours</b>     |                       |                       |                       |                   |
| Number (%) with T<101.0°F (38.3°C) at Hour 24        | 30 (97%)              | 28 (93%)              | 30 (97%)              | 24 (86%)          |
| Time to T<101.0°F (38.3°C) by Hour 24 (hour)*        |                       |                       |                       |                   |
| Mean (SE)  | 3.67 (1.00)           | 4.40 (1.34)           | 3.61 (1.06)           | 8.47 (1.61)       |
| Median   | 1.75                  | 1.13                  | 1.39                  | 5.50              |
| Comparison against placebo, p-value of Log-rank test | p=0.0187              | p=0.0476              | p=0.0137              |                   |

The corresponding survival curve is the Figure 2 on page 59 of the report for Study 004.

### 2. Study 006

#### Survival curves for fever reduction to temperature <100.0°F and <99.0°F in 24 hours from the start of infusion

Please provide information on the number and percentage of patients in the ITT population who had temperature reducing to <100.0°F and to <99.0°F, respectively, in 24 hours in a similar way as specified above.

## Pain studies

### Study 008a and 008b

#### 1. Explanation for data inconsistency and submission of accurate data

Please explain why data in the original study reports were not consistent with data submitted on January 19, 2009 for dropouts per reason per treatment group (not counting resolution of pain and ability to tolerate pain medication by mouth as reasons for dropouts) and for protocol violation/deviation (refer to examples below). Dropout data should be summarized in terms of the number and percentage of patients. Protocol violation/deviation should be summarized in terms of number of cases (there may be multiple violations by the same patient), total number of violations and total number (and percentage) of patients with protocol violation/deviation per treatment group.

#### Examples of data inconsistency

Table 12 on page 52 of the study report for 008a in the original submission had the following content (not counting resolution of pain and ability to tolerate pain medication by mouth as reasons for dropouts)

| Study 008a<br>Patient Disposition    | Placebo<br>(n=134) | 400 mg IVIb<br>(n=134) | 800 mg IVIb<br>(n=138) | Total<br>(n=406) |
|--------------------------------------|--------------------|------------------------|------------------------|------------------|
| All Treated Patients                 | 134                | 134                    | 138                    | 406              |
| <b>Discontinued n (%)</b>            | <b>34?</b>         | <b>35?</b>             | <b>25?</b>             | <b>94?</b>       |
| Reason for discontinuation           |                    |                        |                        |                  |
| Adverse Event                        | 9 (7%)             | 8 (6%)                 | 6 (4%)                 | 23 (6%)          |
| Treatment failure                    | 11 (8%)            | 7 (5%)                 | 4 (3%)                 | 22 (5%)          |
| Withdrawal at patient's request      | 4 (3%)             | 5 (4%)                 | 0                      | 9 (2%)           |
| Inadequate IV Access                 | 3 (2%)             | 1 (<1%)                | 2 (1%)                 | 6 (1%)           |
| Physician request for safety reasons | 1 (<1%)            | 0                      | 1 (<1%)                | 2 (<1%)          |
| Other                                | 6 (4%)             | 14 (10%)               | 12 (9%)                | 32 (8%)          |

Table 1 on page 1 of the January 19, 2009 submission had the following:

| Study 008a<br>Patient Disposition | Placebo<br>(n=134) | 400 mg IVIb<br>(n=134) | 800 mg IVIb<br>(n=138) | Total<br>(n=406) |
|-----------------------------------|--------------------|------------------------|------------------------|------------------|
| All Treated Patients              | 134                | 134                    | 138                    | 406              |
| <b>Discontinued n (%)</b>         | <b>?</b>           | <b>?</b>               | <b>?</b>               | <b>?</b>         |
| Reason for discontinuation        |                    |                        |                        |                  |
| Adverse Event                     | 7                  | 10                     | 7                      | 24               |
| Treatment failure                 | 7                  | 6                      | 2                      | 15               |
| Withdrawal at patient's request   | 3                  | 1                      | 0                      | 4                |
| Noncompliance with protocol       | 0                  | 2                      | 2                      | 4                |
| Inadequate IV Access              | 1                  | 0                      | 0                      | 1                |
| Concurrent illness                | 1                  | 0                      | 0                      | 1                |

#### Another example of data inconsistency

The table below summarized data described in the paragraphs on pages 53-54 and in Table 13 on page 54 of the report for Study 008a in the original submission.

#### Table Summary of Protocol Deviations

| Study 008a<br>Protocol deviations                              | 400 mg IVIb<br>(n=134) | 800 mg IVIb<br>(n=138) | Placebo<br>(n=134) | Total<br>(n=406) |
|--|------------------------|------------------------|--------------------|------------------|
| Total number of patients with major protocol deviations, n (%) | ?                      | ?                      | ?                  | ?                |

|  |     |     |     |      |
|--|-----|-----|-----|------|
| <b>Total number of major protocol deviations</b>               | 88  | 95  | 86  | 269  |
| CTM administration error (outside $\pm 60$ min window)         | 48  | 46  | 49  | 143  |
| Received restricted concomitant medication                     | 28  | 37  | 23  | 88   |
| Exclusion criteria   | 6   | 5   | 6   | 17   |
| Consenting error (timing)                                      | 3   | 6   | 5   | 14   |
| Randomization error (to wrong strata)                          | 3   | 1   | 3   | 7    |
| Total number of patients with minor protocol deviations, n (%) | ?   | ?   | ?   | ?    |
| <b>Total number of minor protocol deviations</b>               | ?   | ?   | ?   | ?    |
| Early day 14 assessment  | 9   | 8   | 8   | 25   |
| Miss-timed assessment  | 376 | 416 | 379 | 1171 |
| Not meeting eligibility criteria                               | 2   | 1   | 0   | 3    |

Table 2 on pages 1-3 of the January 19, 2009 submission had the following:

### Table Summary of Protocol Deviations

| Study 008a<br>Protocol deviations                              | 400 mg IV1b<br>(n=134) | 800 mg IV1b<br>(n=138) | Placebo<br>(n=134) | Total<br>(n=406) |
|--|------------------------|------------------------|--------------------|------------------|
| Total number of patients with major protocol deviations, n (%) | ?                      | ?                      | ?                  | ?                |
| <b>Total number of major protocol deviations</b>               | ?                      | ?                      | ?                  | ?                |
| CTM administration error (outside $\pm 60$ min window)         | 47                     | 46                     | 49                 | 142              |
| Received restricted concomitant medication                     | 28                     | 37                     | 23                 | 88               |
| Exclusion criteria   | 6                      | 5                      | 5                  | 16               |
| Consenting error (timing)                                      | 3                      | 6                      | 5                  | 14               |
| Randomization error (to wrong strata)                          | 3                      | 1                      | 0                  | 4                |
| Total number of patients with minor protocol deviations, n (%) | ?                      | ?                      | ?                  | ?                |
| <b>Total number of minor protocol deviations</b>               | ?                      | ?                      | ?                  | ?                |
| CTM administration error                                       | 13                     | 7                      | 7                  | 27               |
| Early day 14 assessment  | 9                      | 8                      | 8                  | 25               |
| Miss-timed assessment  | 373                    | 416                    | 380                | 1169             |
| Not meeting eligibility criteria                               | 2                      | 1                      | 4                  | 7                |

## 2. Baseline pain intensity per treatment group and for the entire study population

Please provide baseline pain intensity for ITT populations for the two analgesic studies if the data were collected.

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/s/

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Kathleen Davies  
6/2/2009 12:01:28 PM  
CSO

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** NDA 22348/Ibuprofen IV - stats IR  
**Date:** Wednesday, March 11, 2009 8:53:01 AM

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Hi Amy,

We have the following request for clarification:

*For study CPI-CL-006, it appears that the variable AUCT24 in the SAS file EFFICACY.XPT is the primary efficacy variable. Table 2.5 in the Clinical Study Report, however, lists different values for this variable. Clarify why the two sources list different values.*

If you have any questions, let me know.

Kathleen

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** NDA 22-348 IV ibuprofen  
**Date:** Wednesday, March 04, 2009 12:49:06 PM

---

Hi Amy,

Please refer to NDA 22-348 for Ibuprofen IV. I wanted to know that the Agency received the submission for the alternate trade name and it is currently under review with OSE.

We also have a statistical IR for you:

***On page 52 of the report for study CPI-CL-008A, you state, "Eleven patients were randomized to an incorrect stratum." On page 56, however, you state, "All seven randomization errors were errors in stratification where participants were inadvertently assigned to the wrong strata." Further, in the report for CPI-CL-008B (p. 47), you state "there were three patients randomized to incorrect stratification categories."***

***Provide the ID numbers, strata used for randomization, and corrected strata for the subjects who were assigned to the wrong strata in these studies.***

If you have any questions, let me know.

Thanks,

Kathleen



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-348

Cumberland Pharmaceuticals  
2525 West End Avenue, Suite 950  
Nashville, TN 37203

Attention: Amy Rock, PhD  
Senior Manager, Regulatory Affairs

Dear Dr. Rock:

Please refer to your new drug application (NDA) dated December 3, 2008, received December 11, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Ibuprofen Injection.

We also refer to your submissions dated January 12, 19, and 28, and February 4, 2009.

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

Your drug product specifications for [REDACTED] (b) (4) and "any other" impurity exceeds the ICHQ3B qualification threshold of NMT 0.15% for a total daily dose of greater than 2 g. Reliance upon the pharmacopeia standards alone does not justify the safety of this level of impurity. As noted in the preNDA meeting minutes dated June 27, 2008, if the specifications cannot be tightened, you must provide an adequate toxicological risk assessment to justify the safety of the proposed specifications.

We are providing the above comment 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.

**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 indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a waiver of pediatric studies for this application if a Pediatric Written Request (PWR) is not issued by the Agency. In addition, we acknowledge receipt of your request for a deferral of pediatric studies for this application, if a Pediatric Written Request is issued by the Agency.

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

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/

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Bob Rappaport  
2/24/2009 09:22:50 PM



NDA 22-348

**PROPRIETARY NAME REQUEST  
- UNACCEPTABLE**

Cumberland Pharmaceuticals Inc.  
2525 West End Avenue, Suite 950  
Nashville, TN 37203

Attention: Amy Rock, PhD  
Senior Manager, Regulatory Affairs

Dear Dr. Rock:

Please refer to your New Drug Application (NDA) dated December 3, 2008, received December 11, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen for Injection 400mg and 800mg.

We also refer to your December 30, 2008, correspondence, received December 31, 2008, requesting review of your proposed proprietary name, Amelior. We have completed our review of Amelior and have concluded that this name is unacceptable for the following reasons:

We object to the proposed trade name "AMELIOR" because

(b) (4)

(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 proposed trade 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 December 30, 2008. In order to initiate the review of the alternate proprietary name,

Caldolor, submit a new complete request for proprietary name review within 14 days of this letter. 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, call Chris Wheeler, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0151. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kathleen Davies, at (301) 796-2205.

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 of Drug Evaluation and Research

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/s/

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Bob Rappaport  
2/17/2009 02:21:46 PM



NDA 22-348

**PRIORITY REVIEW DESIGNATION**

Cumberland Pharmaceuticals  
2525 West End Avenue, Suite 950  
Nashville, TN 37203

Attention: Amy Rock, PhD  
Senior Manager, Regulatory Affairs

Dear Dr. Rock:

Please refer to your new drug application (NDA) dated December 3, 2008, received December 11, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Amelior<sup>®</sup> (Ibuprofen Injection).

We also refer to your submissions dated January 12, 19, and 28, 2009.

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 June 11, 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 May 21, 2009.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before February 23, 2009.

NDA 22-348

Page 2

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

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/

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Bob Rappaport  
2/9/2009 08:25:37 PM

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** RE: IV Ibuprofen annotated label and reference listed drugs  
**Date:** Monday, February 02, 2009 2:03:38 PM

---

Hi Amy,

Thank-you for the information.

If Cumberland intends to reference a specific NDA or IND in its label or anywhere within its application, it must be listed as a RLD. Otherwise, you are not permitted to utilize the information, irregardless of whether you feel it is most appropriate for that section of the label.

Please advise as soon as possible whether Cumberland wants to utilize these applications as RLDs or if you intend to revise your labeling to remove these references.

If you have any questions, please let me know.

Kathleen

---

**From:** Amy D. Rock [mailto:arock@cumberlandpharma.com]  
**Sent:** Wednesday, January 28, 2009 4:58 PM  
**To:** Davies, Kathleen  
**Subject:** RE: IV Ibuprofen annotated label and reference listed drugs  
**Importance:** High

Kathleen:

Attached is clarification regarding the additional NDAs/INDs in the annotated label. I am sending this via email, but please review and let me know if this should be formally submitted to the NDA.

Also, please let me know if you have additional questions.

Best,  
Amy

---

**From:** Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]  
**Sent:** Wednesday, January 28, 2009 11:13 AM

**To:** Amy D. Rock

**Subject:** IV Ibuprofen annotated label and reference listed drugs

**Importance:** High

Hi Amy,

Please refer to NDA 22-348 for Ibuprofen Injection. We note in your administrative volume that you plan to reference three NDAs for your application: NDA 20-516, 20-402, and 17-463.

We also note that in your annotated label, you reference additional NDAs and INDs in addition to these 3 NDAs.

The Division would like to understand whether you believe these NDAs and INDs noted in the annotated label are ones you feel are required to support your NDA. Please clarify this as soon as possible so that we can determine whether follow up discussions are needed.

Thanks,  
Kathleen

**From:** [Davies, Kathleen](#)  
**To:** ["Amy D. Rock"](#);  
**Subject:** NDA 22348 - statistical IR  
**Date:** Tuesday, January 27, 2009 3:21:06 PM

---

Hi Amy,

Please refer to NDA 22-348 for Ibuprofen Injection. I have the following information request from the statistical review team:

*Provide the software code used to conduct the statistical analyses for studies CPI-CL-004, CPI-CL-006, CPI-CL-008A, and CPI-CL-008B. Also provide the code used to produce the analysis sets from the tabulation data.*

If you have any questions, please let me know.  
Kathleen

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** NDA 22348/request for drug sample  
**Date:** Tuesday, January 13, 2009 3:49:33 PM

---

Hi Amy,

Please send us a few samples ( e.g., 10 vials each) of the two drug product strengths, 400 mg and 800 mg, for the CMC review team. This can be sent to me directly.

Thanks,

***Kathleen Davies, MS***

Regulatory Health Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Food and Drug Administration  
Center for Drug Evaluation and Research  
10903 New Hampshire Ave  
Bldg. 22 Room 3189  
Silver Spring, MD 20993  
(301) 796-2205 *Office*  
(301) 796-9713 *Fax*

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**From:** Davies, Kathleen  
**Sent:** Friday, January 09, 2009 1:48 PM  
**To:** Fields, Ellen; Fang, Christina L; Lee, David J (CDER); Doddapaneni, Suresh; Mellon, Dan; Wasserman, Adam; Price, Dionne; Norton, Jonathan; Christodoulou, Danae D; Haber, Martin T  
**Subject:** FILE/NDA 22348/Ibuprofen IV/Cumberland/Kathleen -link to slide folder

Hi Ibuprofen Team,

Our filing meeting is on Monday, January 12, at 2:30 PM. If you plan to present, please use the slide folder link below to store your slides.

Note, under the new GRMP review process, you will need to present your mid-cycle deliverables as apart of your presentation. I attached the GRMP filing agenda for your reference. Also, please plan to keep your

presentations to roughly 10 minutes at the most so that we have time for all to present and time for any needed discussion.

If you have any questions, let me know.

Thanks,

Kathleen

link:

[\\Cdsnas\pdess1\NDA\NDA 22348\\_Ibuprofen IV\Filing Meeting](#)

From: Davies, Kathleen  
Sent: Monday, January 12, 2009 3:47 PM  
To: 'Amy D. Rock'  
Subject: FW: NDA 22348/Ibuprofen IV/Cumberland

Importance: High

Attachments: n22348 infor request to applicant 1-09.doc

Hi Amy,

Please refer to NDA 22348 for Ibuprofen IV. We have a request (attached) that we request your prompt response to. It will assist us in determining the appropriate sites for inspection for this NDA review.

Kathleen

**For the Applicant:**

**I. Please fill out the tables below**

**1. Pain study 008a**

**1) Dropouts per reason per site**

| Study 008a                                   | Placebo     |               | 400 mg IVIb |        | 800 mg IVIb |        |
|--|-------------|---------------|-------------|--------|-------------|--------|
|  | #patients   | Site #        | #patients   | Site # | #patients   | Site # |
| Resolution of Pain                           | 3<br>2<br>4 | 1<br>12<br>17 |             |        |             |        |
| Ability to tolerate pain medication by mouth |             |               |             |        |             |        |
| No Intravenous access                        |             |               |             |        |             |        |
| Physician request for safety reasons         |             |               |             |        |             |        |
| Withdrawal at patient's request              |             |               |             |        |             |        |
| Discontinued secondary to AE                 |             |               |             |        |             |        |
| Treatment Failure                            |             |               |             |        |             |        |
| Other - (give specific reason)               |             |               |             |        |             |        |
| Other - (give specific reason)               |             |               |             |        |             |        |

**2) Protocol deviations per reason per site**

| Study 008a   | Placebo     |               | 400 mg IVIb |        | 800 mg IVIb |        |
|--|-------------|---------------|-------------|--------|-------------|--------|
|  | #patients   | Site #        | #patients   | Site # | #patients   | Site # |
| <b>Major Protocol Deviations</b>                   |             |               |             |        |             |        |
| Consenting   | 1<br>1<br>1 | 1<br>12<br>17 |             |        |             |        |
| CTM administration                                 |             |               |             |        |             |        |
| Exclusion criteria                                 |             |               |             |        |             |        |
| Received restricted concomitant medications        |             |               |             |        |             |        |
| Randomization                                      |             |               |             |        |             |        |
| Total  |             |               |             |        |             |        |
| <b>Minor Protocol Deviations</b>                   |             |               |             |        |             |        |
| Day 14 follow-up:                                  |             |               |             |        |             |        |
| Missed pain assessment (nocturnal awakenings)      |             |               |             |        |             |        |
| Missed pain assessment (other reason)              |             |               |             |        |             |        |
| Miss-timed pain assessment                         |             |               |             |        |             |        |
| Inaccurate recording of timing for use of morphine |             |               |             |        |             |        |
| Missed discharge assessments (VS, labs)            |             |               |             |        |             |        |
|  |             |               |             |        |             |        |
|  |             |               |             |        |             |        |
| Inclusion Criteria Not Met                         |             |               |             |        |             |        |



## 2. Pain Study 008b

### 1 ) Dropouts per reason per site

| Study 008b                           | Placebo   |        | 800 mg IVIb |        |
|--------------------------------------|-----------|--------|-------------|--------|
|                                      | #patients | Site # | #patients   | Site # |
| Resolution of Pain                   | 1         | 3      |             |        |
|                                      | 1         | 9      |             |        |
| Intravenous access discontinued      |           |        |             |        |
| Physician request for safety reasons |           |        |             |        |
| Withdrawal at patient's request      |           |        |             |        |
| Discontinued secondary to AE         |           |        |             |        |
| Treatment Failure                    |           |        |             |        |
| Other - (give specific reason)       |           |        |             |        |
| Other - (give specific reason)       |           |        |             |        |

### 2) Protocol violations/deviations per reason per site

| Study 008b  | Placebo   |        | 800 mg IVIb |        |
|---|-----------|--------|-------------|--------|
|   | #patients | Site # | #patients   | Site # |
| <b>Protocol violations</b>                            |           |        |             |        |
| Eligibility Criteria Not Met                          | 1         | 1      |             |        |
|   | 1         | 12     |             |        |
|   | 1         | 17     |             |        |
| Restricted medication in 24 hours before initial dose |           |        |             |        |
| Dosing time deviation                                 |           |        |             |        |
| <b>Protocol Deviations</b>                            |           |        |             |        |
| Missed (or incomplete screening/baseline assessments) |           |        |             |        |
| Use restricted medication during treatment            |           |        |             |        |
| Morphine use recorded outside 30 minute window        |           |        |             |        |
| Vital signs outside a +/- 60 minute window,           |           |        |             |        |
| Pain scores measured outside a +/- 60 minute window   |           |        |             |        |
| Miss timed VAS and/or RASS assessments                |           |        |             |        |
| Miss timed clinical lab tests                         |           |        |             |        |
| Incomplete clinical labs                              |           |        |             |        |
| Discharge labs miss timed or incomplete               |           |        |             |        |
| Other-specific.                                       |           |        |             |        |
| Other-specific  |           |        |             |        |



5. Please summarize exposure information in terms of number of subjects/patients exposed in the same format as the table shown below for PK studies, efficacy studies and for all the subjects receiving IV ibuprofen in the NDA.

| Number of doses exposed | 200 mg IVIb | 400 mg IVIb | 800 mg IVIb | Total |
|-------------------------|-------------|-------------|-------------|-------|
| 1                       |             |             |             |       |
| 2                       |             |             |             |       |
| 3                       |             |             |             |       |
| 4                       |             |             |             |       |
| 5                       |             |             |             |       |
| 6                       |             |             |             |       |
| 7                       |             |             |             |       |
| 8                       |             |             |             |       |
| 9                       |             |             |             |       |
| 10                      |             |             |             |       |
| 11                      |             |             |             |       |
| 12                      |             |             |             |       |
| 13                      |             |             |             |       |
| 14                      |             |             |             |       |
| 15                      |             |             |             |       |
| 16                      |             |             |             |       |
| 17                      |             |             |             |       |
| 18                      |             |             |             |       |
| 19                      |             |             |             |       |
| 20                      |             |             |             |       |

| Number of days exposed | 200 mg IVIb | 400 mg IVIb | 800 mg IVIb | Total |
|------------------------|-------------|-------------|-------------|-------|
| 1                      |             |             |             |       |
| 2                      |             |             |             |       |
| 3                      |             |             |             |       |
| 4                      |             |             |             |       |
| 5                      |             |             |             |       |

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

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Kathleen Davies  
6/2/2009 11:59:35 AM  
CSO

**From:** Davies, Kathleen  
**To:** "Amy D. Rock";  
**Subject:** NDA 22348/Ibuprofen Injection - IR request  
**Date:** Thursday, January 08, 2009 11:15:20 AM

---

Hi Amy,

Please refer to NDA 22-348 for Ibuprofen Injection. The statistical review team has the following requests for information upon initial review of the NDA:

*Provide efficacy analysis data sets for studies CPI-CL-004 and CPI-CL-006. These files should have one record per subject and include, but not be limited to, the following variables: primary and secondary endpoints, treatment arm, stratification factors, covariates used in the analysis, demographic subgroups (age, race, sex), and membership in the intent-to-treat and other analysis sets. The definition file ("define.pdf") should indicate which variables in the tabulation data were used to derive the analysis variables.*

*Provide prospective statistical analysis plans for studies CPI-CL-004 and CPI-CL-006.*

If you have any questions, please let me know.

Kind Regards,

Kathleen



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 62,605

Cumberland Pharmaceuticals  
2525 West End Avenue, Suite 950  
Nashville, TN 37203

Attention: Amy Rock, Ph.D.  
Regulatory Affairs

Dear Dr. Rock:

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

We also refer to the meeting between representatives of your firm and the FDA on May 29, 2008. The purpose of the meeting was to discuss your planned New Drug Application (NDA).

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) 796-2205.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** May 29, 2008

**TIME:** 11:00 AM – 12:00 PM (EST)

**LOCATION:** Food and Drug Administration, Bldg. 22, Room 1313  
10903 New Hampshire Ave., Silver Spring, MD 20993-0002

**APPLICATION:** IND 62,605

**PRODUCT:** Ibuprofen Injection

**INDICATION:** Relief of pain and reduction in fever

**SPONSOR:** Cumberland Pharmaceuticals, Inc.

**TYPE OF MEETING:** Type B (pre-NDA)

**MEETING CHAIR:** Sharon Hertz, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

**MEETING RECORDER:** Kathleen Davies, MS, Regulatory Health Project Manager

| <b>FDA Attendees</b>     | <b>Title</b>  |
|--------------------------|---|
| Bob Rappaport, MD        | Director, Division of Anesthesia, Analgesia and Rheumatology Products |
| Sharon Hertz, MD         | Deputy Director (Analgesic Team)                                      |
| Christina Fang, MD       | Medical Reviewer  |
| Dan Mellon, PhD          | Pharmacology Toxicology Supervisor                                    |
| Danae Christodoulou, PhD | Pharmaceutical Assessment Lead  |
| David Lee, PhD           | Clinical Pharmacology Reviewer  |
| Dionne Price, PhD        | Statistical Team Leader   |
| Joan Buenconsejo, PhD    | Statistical Reviewer  |
| Kathleen Davies, MS      | Regulatory Health Project Manager                                     |
| Sharon Thomas            | Regulatory Health Project Manager                                     |
| Diana Walker, PhD        | Regulatory Health Project Manager                                     |

| <b>Cumberland Pharmaceuticals Inc.<br/>Attendees</b> | <b>Title</b>                               |
|--|--|
| Gordon Bernard, M.D.                                 | Senior Vice President and Medical Director |
| Leo Pavliv, RPh                                      | Vice President Operations                  |
| Amy Rock, Ph.D.                                      | Senior Manager Regulatory Affairs          |
| Bryan Voss, Ph.D.                                    | Regulatory Affairs Associate               |
| (b) (4)  |  |

**BACKGROUND:**

Cumberland Pharmaceuticals Inc. submitted a Type B meeting request to discuss their planned NDA. Cumberland Pharmaceuticals, Inc. plans to submit a 505(b)(2) application in eCTD format.

Each of the Sponsor's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the firm on May 28, 2008.

*Question 1: Cumberland has contracted with (b) (4) to submit our 505(b)(2) NDA in eCTD format. Due to the multiple eCTD submissions generated by (b) (4) does the Agency agree that a pilot application is not necessary?*

**FDA Response:**

**If you intend to submit your NDA in eCTD format, the Division encourages you to contact the eCTD review team ([esub@fda.hhs.gov](mailto:esub@fda.hhs.gov)) and to utilize the information provided on the FDA website for electronic submissions (<http://www.fda.gov/cder/regulatory/ersr/ectd.htm>).**

**Discussion:**

The Sponsor stated that they do not intend to submit a pilot eCTD application and asked the Division if they had any comment regarding this decision. The Division stated that the Sponsor could choose not to submit a pilot application if they were confident in their contractor; however, it was critical to note that if there are any issues with their eCTD NDA submission, it can be a filing issue. The Sponsor acknowledged this advice and stated they still intend not to submit a pilot eCTD application.

*Question 2: Cumberland intends to incorporate all safety data from Cumberland conducted clinical trials (utilizing the Cumberland formulation of intravenous ibuprofen) for presentation in the integrated summary of safety (ISS) and all efficacy data from Cumberland conducted clinical trials for presentation in the integrated summary of efficacy (ISE) by indication (fever or pain). Cumberland intends to present the legacy study conducted under investigator IND (b) (4) as support for safety and efficacy only in the clinical overview and summary. A different formulation of intravenous ibuprofen was used in this study in a patient population and indication that is very different from that studied in Cumberland conducted clinical trials. IND (b) (4) evaluated the efficacy of intravenous ibuprofen in reducing mortality in patients with severe septic shock. The mortality rate in this patient population is very high, typically over 50%. Cumberland believes that including this data in the ISS would not allow for a clear and accurate interpretation of the safety of Cumberland's intravenous ibuprofen in the target populations. Does the Agency agree that it is not appropriate to include this legacy study in the ISS or ISE, but rather as support in the clinical overview and summary?*

**FDA Response:**

Your proposal to present the data collected under IND (b) (4) separately from the data collected under IND 62,605 is acceptable, but the data should be presented in the ISS and not just in a study report.

Discussion:

There was no further discussion on this point.

*Question 3: Cumberland intends to submit SAS XPORT (Version 5) transport files for datasets from the pivotal pain studies (CPI-CL-008A and CPI-CL-008B) and pivotal fever studies (CPI-CL-004 and CPI-CL-006). Does the Agency agree that the SAS datasets from only these studies should be provided? Would the Agency provide input as to whether SAS programs should be included with relevant datasets?*

**FDA Response:**

Your proposal to submit individual datasets for the pain and fever studies is acceptable.

**Submit the raw and derived (i.e., analysis-ready) datasets for each study and include a data definition file (i.e., define.pdf) for each dataset. In the data definition file, link the variable names (i.e., raw data) to a sample case report form. Provide an explanation/derivation for all the derived variables.**

**You do not need to submit the SAS programs; however, we may request them during review of the NDA.**

Discussion:

There was no further discussion on this point.

*Question 4: Cumberland intends to submit case report forms associated with patient deaths and serious adverse events from each Cumberland sponsored clinical study. Does the Agency agree that these are the appropriate case report forms to include in the NDA submission?*

**FDA Response:**

**In addition, submit the case report forms for all discontinuations due to adverse events, as well as those due to “other” and “patient request.” Provide the case report forms for the (b) (4) study as well as patient narratives for all of the serious adverse events including deaths.**

Discussion:

There was no further discussion on this point.

*Question 5: Reference is made to Cumberland study (b) (4)*

(b) (4)

[Redacted text block]

(b) (4)

The determination of [Redacted text]

[Redacted text block]

[Redacted text block]

Discussion:

(b) (4)

[Large redacted text block]

(b) (4)

*Question 6: Reference is made to pivotal studies CPI-CL-008A and CPI-CL-008B. Both studies met their primary endpoint demonstrating a statistically significant reduction in morphine use in post-surgical patients receiving Ibuprofen Injection compared to those receiving placebo. The data from these studies are not normally distributed. Appropriate statistical testing for normality and analyses (log transformation as specified in the statistical analysis plan (attached in Appendix A)) will be presented in the final study report. Further, an additional transformation, the Box-Cox transformation, was applied for robustness of analysis. Does the agency agree that including the log transformation and Box-Cox transformation would be adequate to provide in the NDA?*

**FDA Response:**

**Yes, provide the results from all analyses in the NDA.**

**Discussion:**

There was no further discussion on this point.

*Question 7: Cumberland will submit batch records, stability data and process validation batch information for a 400mg (b) (4) vial, 4mL fill) vial in the NDA. The product remains stable with negligible changes in the purity profile and other stability parameters through at least 4 years at 25°C and 6 months at 40°C. Cumberland intends to also manufacture an 800mg vial using the identical formulation and using an identical manufacturing process but with an 8mL fill into a 10mL vial. The vial will also be a type 1 glass vial and the stopper. the same fluoropolymer coated stopper formulation supplied by (b) (4). The 800mg vial will initially be manufactured by an alternative manufacturer, (b) (4) and will also likely be manufactured by (b) (4) at a site in the United States in addition to possibly being manufactured by the current (b) (4). Since the products are essentially identical with the exception of fill volume will the agency accept one month of stability data from (b) (4) assuming the stability data are comparable? Additional stability data could be submitted during review of the NDA, if required.*

**FDA Response:**

We do not agree. We note that the head space is different in the two dosage strengths.

For the 800-mg strength, provide at least 3-months stability data under long-term and accelerated storage on one batch from each proposed commercial site. Expiration dating of the 800-mg strength will be assessed as per ICH Q1E, based on available real time data, and statistical analysis, as applicable.

We strongly recommend that you submit the stability data in the NDA. While every effort will be made to review the proposed amendment to the NDA, its review will depend on the timeliness of submission, extent of submitted data and available resources. Therefore, and as per GRMP guidelines, we may not be able to review any amendment submitted to the NDA during the review cycle.

Discussion:

The Sponsor stated that studies have been completed using nitrogen headspace and air headspace and no change in stability was noted. The Sponsor asked if this data would be adequate to link the 800-mg product in a (b) (4) vial to the 400-mg product in a (b) vial. The Division stated that, if the Sponsor could provide bridging data and supporting stability data, then it will be a review issue. Bridging stability data can be submitted on development batches. The Division requested at least 3 months stability data under normal and accelerated storage with the NDA submission.

*Question 8: Cumberland has registered the trade name Amelior<sup>®</sup> and intends to submit this trade name for Agency review: Amelior<sup>®</sup> (ibuprofen) Injection. Can the agency confirm that this trade name is acceptable for use?*

**FDA Response:**

The proposed trade name will be submitted for consultative review to the Office of Surveillance and Epidemiology at the time of your NDA submission. Acceptability of the trade name will be communicated upon filing of the NDA during the review cycle.

Discussion:

The Sponsor asked when during the NDA review they would be notified of the acceptability of their proposed trade name, Amelior<sup>®</sup>. The Division explained that acceptability of a trade name is generally determined after filing an application; however, the trade name must be reviewed again 90 days prior to taking action on an NDA application.

**We also provide the following guidance regarding your planned NDA:**

**REGULATORY**

We recommend 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/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408

(available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

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

**Discussion:**

The Sponsor requested an explanation of the importance of the listed drug and what would need to be referenced to a listed drug. The Division explained that the Sponsor must cite all listed drugs used to support all aspects of their application. Anything that the Sponsor intends to incorporate into their label must be referenced and patent certified. This includes gaining patent certification for any cited literature references that contain a branded drug. The Division strongly urged the Sponsor to utilize the referenced guidance and citizen petition noted above in planning their submission to ensure they have adequately addressed all referenced information in their planned NDA.

**NONCLINICAL**

**Although your meeting package does not contain any information related to your nonclinical development plan, the following recommendations are provided that pertain the non-clinical section of the NDA submission:**

- 1. You have not stated which product(s) you intend to rely upon to support your NDA application. As noted above, you must provide clear justification that establishes how the data you intend to reference is scientifically appropriate to support your product. Your NDA submission must clearly indicate what information you are relying upon to fulfill the nonclinical requirements for your 505(b)(2) application.**
- 2. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Adequate qualification must include:**
  - a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies e.g. one Ames assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**
  - b. Repeat dose toxicology of appropriate duration to support the proposed indication.**

- c. **Potentially genotoxic impurities or degradation products pose an additional risk, therefore, a specification of NMT (bb) mcg/day should be set for genotoxic or potentially genotoxic residual intermediates in the (b) (4) scheme unless otherwise justified.**
3. **The format of package insert should follow the guidelines for PLR format as per Federal Register Notice dated January 24, 2006. The non-clinical section of the label must be updated with respect to mutagenicity, fertility information as well as information on pregnancy, labor and delivery.**
4. **Final reports of all nonclinical data such as 28-day IV toxicity study, vein irritation, hemolysis and flocculation tests using the proposed marketing formulation must be provided in the NDA.**
5. **A summary of non-clinical safety and toxicity of ibuprofen must be presented in the NDA. Copies of all referenced citations must be provided in the NDA submission.**
6. **The NDA submission must contain information on potential leachables and extractables from the drug container closure system. Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).**

Discussion:

There was no further discussion on these points.

#### **CMC**

**Provide a complete list of the manufacturing facilities, including full addresses, cGMP compliance status and whether they are ready for inspection, in the NDA. For any foreign facilities, provide a name contact and telephone number at the site.**

Discussion:

There was no further discussion on this point.

#### **CLINICAL**

**The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.**

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 5.3 Exposure-Response Relationships - important exposure-response assessments.
3. Section 7.1.6 - Less common adverse events (between 0.1% and 1%).
4. Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.1.8.3.2 - Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.1.8.3.3 - Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.1.9.3. – Standard analyses and explorations of ECG data.
12. Section 7.1.16 – Overdose experience.
13. Section 7.4.2.1 - Explorations for dose dependency for adverse findings.
14. Section 7.4.2.2 - Explorations for time dependency for adverse findings.
15. Section 7.4.2.3 - Explorations for drug-demographic interactions.
16. Section 7.4.2.4 - Explorations for drug-disease interactions.
17. Section 7.4.2.5 - Explorations for drug-drug interactions.
18. Section 8.2 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

We recommend the following for the submitted datasets:

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.
2. The integrated safety dataset that should include the following fields/variables:
  - a. A unique patient identifier
  - b. Study/protocol number
  - c. Patient's treatment assignment
  - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
  - e. Dosing at time of adverse event
  - f. Dosing prior to event (if different)
  - g. Duration of event (or start and stop dates)
  - h. Days on study drug at time of event
  - i. Outcome of event (e.g. ongoing, resolved, led to discontinuation)
  - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
  - k. Marker for serious adverse events
  - l. Verbatim term
3. The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form.
4. In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.
5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Please provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

7. Please perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, please provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. Also, for the concomitant medication dataset, you should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format.
11. Please perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. In every dataset, all dates should be formatted as ISO date format.
13. Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.
14. All datasets should contain the following variables/fields (in the same format and coding):
  - a. Each subject should have one unique ID across the entire NDA
  - b. Study number
  - c. Treatment assignment
  - d. Demographic characteristics (age, race, gender, etc.)

A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and

**“low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.**

**Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.**

**For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.**

**If you and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).**

Discussion:

The Sponsor requested clarification as to whether postmarketing surveillance was limited to only their IV Ibuprofen product. The Division confirmed that any postmarketing surveillance that the Sponsor is responsible for is limited only to their product.

### **Common PLR Labeling Deficiencies**

#### **Highlights:**

- 1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]**
- 2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]**
- 3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].  
[See 21 CFR 201.57(a)(1)]**
- 4. The drug name must be followed by the drug’s dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]**

5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement “See full prescribing information for complete boxed warning.” Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:  
  
“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”  
  
Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
8. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
9. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
10. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
11. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
12. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
13. A horizontal line must separate the Highlights, Contents, and FPI.

[See 21 CFR 201.57(d)(2)]

**Contents (Table of Contents):**

14. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
15. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
16. Create subsection headings that identify the content. Avoid using the word **General, Other, or Miscellaneous** for a subsection heading.
17. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
18. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under **Use in Specific Populations**, subsection 8.2 (**Labor and Delivery**) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

19. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of the Contents:  
“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information (FPI):**

20. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
21. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.

22. Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
23. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
24. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
25. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
26. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
27. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
28. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
29. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
30. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels

and carton labeling. [See **Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements**]. The same applies to PPI and MG.

31. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
32. Refer to the Institute of Safe Medication Practices' website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

Discussion:

There was no further discussion on the PLR comments.

**CDISC Data Requests to Sponsors  
Quantitative Safety and Pharmacoepidemiology Group**

**Safety Analysis Plan**

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis ([www.cdisc.org](http://www.cdisc.org)).

At a minimum the Safety Analysis Plan should address the following components:

- a. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- b. Safety endpoints for Adverse Events of Special Interest (AERI)
- c. Definition of Treatment Emergent Adverse Event (TEAE)
- d. Expert adjudication process (Expert Clinical Committee Charter)
- e. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- g. When unanticipated safety issues are identified the QSAP may be amended.

### **Study Data Tabulation Model (SDTM) Issues**

- 1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)**
- 2. Domains**
  - a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.**
    - (DV) Protocol deviations
    - (DA) Drug Accountability
    - (PC, PP) Pharmacokinetics
    - (MB, MS) Microbiology
    - (CF) Clinical Findings
  - b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.**
    - Tumor information
    - Imaging Data
    - Complex Inclusion/Exclusion Criteria
- 3. Variables**
  - a. All required variables are to be included.**
  - b. All expected variables should be included in all SDTM datasets.**
  - c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.**
  - d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.**
  - e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.**
  - f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.**

4. **Specific issues of note:**
  - a. **SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.**
  - b. **Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.**
  - c. **These issues can be addressed through the request for ADaM datasets**

#### **Analysis Data Model (ADaM) Issues**

1. **Please specify which ADaM datasets you intend to submit.**
2. **Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.**
3. **Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.**
4. **Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.**
5. **Please indicate which core variables will be replicated across the different datasets, if any.**
6. **SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.**

#### **General Items**

##### **Controlled terminology issues**

- a. **Please use a single version of MedDRA for a submission. Does not have to be most recent version**
- b. **We recommend that the WHO drug dictionary be used for concomitant medications.**
- c. **Please refer to the CDISC terminology for lab test names.**

- d. **Issues regarding ranges for laboratory measurements should be addressed.**

Discussion:

There was on further discussion on the CDISC comments.

**ACTION ITEMS:**

1. The Sponsor will submit a rationale for a link between adult PK data and pediatric PK data prior to the NDA submission for the Division to review and provide feedback.
2. The Sponsor understands that if upon review no link between pediatric and adult data is established, that they (b) (4).
3. The Sponsor will have at minimum 3 months stability data for their product at the time of submission.
4. The Sponsor understands that they must cite all RLDs that support any aspect of their planned NDA submission.

Linked Applications

Sponsor Name

Drug Name

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IND 62605

-----  
CUMBERLAND  
PHARMACEUTICALS  
INC

-----  
IBUPROFEN INJECTION

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/s/

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KATHLEEN M DAVIES

06/27/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 62,605

Cumberland Pharmaceuticals Inc.  
2525 West End Ave., Ste. 950  
Nashville, TN 37203

Attention: Amy Rock, PhD  
Regulatory Affairs

Dear Dr. Rock:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 15, 2005. The purpose of the teleconference was to obtain FDA's agreement of the statistical analysis plans for three protocols currently being conducted under the IND.

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, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, MD  
Director  
Division of Anesthesia, Analgesia  
Rheumatology Products, HFD-170  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure



## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** July 15, 2005

**TIME:** 11:30 am – 12 noon

**LOCATION:** S300, 9201 Corporate Boulevard, Rockville, MD

**APPLICATION (DRUG):** IND 62, 605 (intravenous ibuprofen)

**SPONSOR:** Cumberland Pharmaceuticals, Inc.

**INDICATION:** Treatment of pain and (b) (4) reduction in fever

**TYPE OF MEETING:** Teleconference guidance meeting

**MEETING CHAIR:** Sharon Hertz, MD

**MEETING RECORDER:** Ms. Jane A. Dean, RN, MSN

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

| Name of FDA Attendee      | Title                  | Division Name & HFD#  |
|---------------------------|------------------------|-----------------------|
| 1. Sharon Hertz, MD       | Deputy Director        | ODEII, DAARP, HFD-170 |
| 2. James Witter, MD, PhD  | Medical Team Leader    | ODEII, DAARP, HFD-170 |
| 3. Christina Fang, MD     | Medical Reviewer       | ODEII, DAARP, HFD-170 |
| 4. Tom Permutt, PhD       | Statistics Team Leader | OB, DBIII, HFD-725    |
| 5. Lisa Kammerman, PhD    | Statistics Reviewer    | OB, DBIII, HFD-725    |
| 13. Jane A. Dean, RN, MSN | Project Manager        | ODEII, DAARP, HFD-170 |

### EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

| External Attendee  | Title                                | Sponsor                    |
|--------------------|--------------------------------------|----------------------------|
| 1. AJ Kazimi       | CEO                                  | Cumberland Pharmaceuticals |
| 2. Leo Pavliv, RPh | VP - Operations                      | Cumberland Pharmaceuticals |
| 3. Amy Rock, PhD   | Senior Scientist, Regulatory Affairs | Cumberland Pharmaceuticals |
| 4. (b) (4)         | (b) (4) Consultant                   | (b) (4)                    |

**PURPOSE OF THE MEETING:** The purpose of the meeting was to obtain final agreement with the FDA regarding the statistical analysis plans for:

1. Clinical study CPI-CL-004, "A Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Ibuprofen Injection in Adult Febrile Patients;"

2. (b) (4) [REDACTED]  
[REDACTED] s," and
3. Clinical study CPI-CL-008, "*A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection (IVIb) for Treatment of Pain in Post-Operative Adult Patients.*"

**MEETING OBJECTIVES:** The meeting objective is the same as the purpose of the meeting.

**BACKGROUND:** On June 14, 2004, the Sponsor submitted a Special Protocol Assessment (SPA) of the protocol titled *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection (IVIb) for Treatment of Pain in Post-Operative Adult Patients.* The Division provided a response via a teleconference on July 28, 2004 addressing the following points of discussion:

1. Subjects with a sensitivity to aspirin should be excluded from participation;
2. Follow-up should be extended to two weeks;
3. If a related adverse event occurs, patients should be followed to resolution;
4. The rationale for the age range selected will be provided;
5. Clarification that the objective of the study was to demonstrate not that the drug product will preempt pain, but that it would decrease pain as evidenced by a lower requirement for morphine use;
6. An amendment would be sent to the protocol that clarified the statistical definition of "Intent to Treat" and how imputation of missing data would be handled statistically.

The Sponsor subsequently amended their statistical analysis plan based on the Division's response. They included additional methods for imputing missing data, and for robustness, sensitivity analysis would be performed using a more conservative approach for imputing missing data. Furthermore, the Sponsor provided clarification regarding the administrative interim analysis. They also clarified that the objective of the interim analysis without breaking the blind was to get an estimate of standard deviation of the primary efficacy parameter to adjust the sample size, if necessary to ensure adequate power for the study. They additionally have proposed processes and procedures to ensure the integrity of the trial.

**QUESTIONS:** The Sponsor's question was related to the three protocols mentioned above. Does the agency agree that the draft statistical analysis plan is adequate for data analysis for these studies? The Division's response is captured in the Meeting Comments that follow.

**MEETING COMMENTS:**

For Clinical Study CPI-CL-004, the Division recommended that the Sponsor adjust the analysis for variables (i.e., by center and by disease severity) used to stratify the randomization. The Division also asked that the Sponsor pay particular attention to the cardiovascular (CV) parameters, to capture CV events that occur and to describe the results in the NDA submission.

(b) (4)



For Clinical Study CPI-CL-008, the Division confirmed with the Sponsor that Part A and Part B would be analyzed separately, the interim analysis would be used to estimate the accuracy of their sample size and that the study would remain blinded. If the analysis suggests more patients are needed for statistical evaluation, study size would be increased. In any event, the sample size would not be decreased. The Division also recommended that the Sponsor adjust the analysis to reflect the variables used to stratify the randomization.

The Sponsor added that a Data Safety Monitoring Board (DSMB) was already in place.

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Sharon Hertz  
8/12/05 12:06:01 PM  
Signing for Bob Rappaport, MD



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 62,605

Cumberland Pharmaceuticals Inc.  
Attention: Amy Rock, PhD  
Regulatory Affairs  
2525 West End Ave., Ste. 950  
Nashville, TN 37203

Dear Dr. Rock:

Please refer to your Investigational New Drug Application IND file for ibuprofen injection.

We also refer to the meeting between representatives of your firm and the FDA on April 23, 2004. The purpose of the meeting was to obtain FDA's input and concurrence into the strategy for registration of intravenous ibuprofen for treatment of (b) (4) and reduction of fever in patients (b) (4).

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, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure



**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** April 23, 2004

**TIME:** 2:35pm – 3:18pm

**LOCATION:** N351, 9201 Corporate Boulevard, Rockville, MD

**APPLICATION (DRUG):** IND 62,605 (ibuprofen injectable)

**SPONSOR:** Cumberland Pharmaceuticals, Inc.

**TYPE OF MEETING:** Guidance (telecon)

**MEETING CHAIR:** Sharon Hertz, MD

**MEETING RECORDER:** Ms. Jane A. Dean, RN, MSN

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:**

| Name of FDA Attendee        | Title                 | Division Name & HFD# |
|-----------------------------|-----------------------|----------------------|
| 1. Brian E. Harvey, MD, PhD | Acting Director       | ODEV/DAAODP, HFD-550 |
| 2. Sharon Hertz, MD         | Deputy Director       | ODEV/DAAODP, HFD-550 |
| 3. James Witter, MD, PhD    | Medical Team Leader   | ODEV/DAAODP, HFD-550 |
| 4. Christina Fang, MD       | Medical Reviewer      | ODEV/DAAODP, HFD-550 |
| 5. Carmen DeBellis, RPh     | Chief Project Manager | ODEV/DAAODP, HFD-550 |
| 6. Carolyn L. Yancey, MD    | Medical Reviewer      | ODEV/DAAODP, HFD-550 |
| 7. Jane A. Dean, RN, MSN    | Project Manager       | ODEV/DAAODP, HFD-550 |

**EXTERNAL CONSTITUENT ATTENDEES AND TITLES:**

| External Attendee      | Title                     | Sponsor/Firm Name          |
|------------------------|---------------------------|----------------------------|
| 1. A. J. Kazimi        | CEO                       | Cumberland Pharmaceuticals |
| 2. Leo Pavliv, RPh     | Vice-President Operations | Cumberland Pharmaceuticals |
| 3. Gordon Bernard, MD  | Medical Director          | Cumberland Pharmaceuticals |
| 4. Tonya Yarbrough, RN | Medical Affairs Manager   | Cumberland Pharmaceuticals |
| 5. Amy Rock PhD        | Regulatory Affairs        | Cumberland Pharmaceuticals |

**PURPOSE OF THE MEETING:** To gain FDA input and concurrence into the strategy for registration of intravenous ibuprofen for treatment of (b) (4) and reduction in fever in patients (b) (4).

**MEETING OBJECTIVES:** To obtain FDA input on the revised clinical development plan and clinical protocols included in the meeting package.

**BACKGROUND:** Ibuprofen injectable is a formulation for reduction of (b) (4) and reduction in fever in patients (b) (4). It is administered as an intravenous infusion approximately every four to six hours, up to 120 hours.

Cumberland Pharmaceuticals participated in a Pre-IND meeting with the FDA on February 10, 2000, obtaining guidance for the sponsor's formulation of intravenous ibuprofen and development of a general investigation plan. On May 4, 2001, Cumberland submitted an Investigational New Drug Application (IND) for ibuprofen injection. The FDA received it on May 7, 2001 and assigned it IND #62,605.

Since the submission of the original IND, a Pre-NDA meeting was held on June 1, 2001 to reach agreement with the FDA regarding the suitability of the available non-clinical and clinical data to support a 505(b)(2) NDA submission as well as discussing pharmacokinetics data and endpoints for the proposed pediatric clinical study. On June 4, 2001, the IND was inactivated per sponsor's request and then reactivated per sponsor's request on July 3, 2001. The sponsor met with the Division on October 22, 2003 to obtain further guidance on their development plan, the adequacy of the completed toxicology studies, and the adequacy of ongoing clinical trials to provide safety and efficacy data for the NDA. Subsequently, a telecon was held on January 8, 2004 at which time additional input was obtained from the FDA on safety data issues. The sponsor requested another telecon to clarify their understanding of the Division's response and the meeting minutes herein include the original draft responses as well as additional meeting comments during the telecon.

#### **SUMMARY OF UNDERSTANDINGS:**

1. The Sponsor agreed to increase the number of subjects to address overall safety.
2. The Sponsor will submit a summary of the 16 serious adverse events to date to the IND.
3. The Sponsor will have the Data Safety Monitoring Board send a confidential summary of data from each treatment group before unblinding takes place.
4. Minutes will be provided by the Division within 30 days of the meeting date.

## **QUESTIONS:**

### **Clinical/Development Plan:**

**Question 1:** Reference is made to the 08 January 2004 meeting between the Division and Cumberland. Due to the concern expressed by the Division for potential off-label use of intravenous ibuprofen for the treatment of pain for more than 24 hours, Cumberland has revised the clinical development plan (included as Appendix A).

**Does the Agency agree that this revised development plan incorporates the necessary clinical studies to support a 505(b)(2) application for the indication of fever and pain in adult (b) (4):**

### **Original FDA Response:**

*Given that you are proposing to submit the NDA as a 505(b)(2) application, and that different patients will be enrolled for parts A and B, the proposed study in postoperative pain may be sufficient to provide adequate support for a finding of efficacy with a positive outcome. The use of opioid sparing as the primary efficacy endpoint to detect analgesia may require a larger enrollment in order to power the study to detect a statistically significant difference between treatment groups. The safety database does not appear to be sufficient to adequately assess any safety concerns that arise from use in the postoperative setting with only 70 patients from clinical trials. The additional 85 patients from use of IV ibuprofen in patients with abdominal surgery may not be more than supportive given the limited information available from literature reports. At least 300 patients with postoperative pain should be exposed to the IV ibuprofen, with a substantial number receiving the highest recommended dose.*

*For the indication of fever reduction, a positive outcome from the ongoing study, CPI-CL-004, in combination with supportive data from study CPI-CL-006 and prior findings of efficacy by the Agency may also be sufficient to provide adequate support for a finding of efficacy.*

### **Meeting Comments:**

*The Division emphasized that active controlled, non-inferiority studies are generally not considered adequate to support a finding of efficacy for an analgesic. A finding of superiority against a comparator is necessary.*

*The Division indicated that it was important to see a broad range of safety data including data from patients who might not be hemodynamically stable. The 300 post operative pain patients do not need to come from a new efficacy trial. The Sponsor indicated that there was safety data from the (b) (4) trial, in which approximately 60% of patients were in shock, and from the post-op study, in which approximately 20% of patients underwent surgery related to repair of traumatic injuries.*

*The Division expressed concern about basing intravenous dosing on oral dosing given the different patient populations that may be exposed in a clinical setting with an intravenous*

*formulation. The Division requested the Sponsor provide clarification regarding what would be considered clinically meaningful outcomes in reduction in opioid use and reduction in fever.*

**Question 2:** Reference is made to the 08 January 2004 meeting between the Division and Cumberland. Due to the concern expressed by the Division for potential off-label use of intravenous ibuprofen for the treatment of pain, Cumberland is proposing two pain studies, conducted under a single protocol (included as Appendix B).

**Does the Agency agree that if the product is shown to be safe and effective in the proposed pain study that no additional pain studies will be required to obtain approval for a pain indication as part of a 505(b)(2) application?**

**Original FDA Response:**

*Depending on the number of patients enrolled in the efficacy trial, additional open-label exposure may be necessary to complete the safety database.*

**Meeting Comments:** *None*

**Question 3:** Cumberland is proposing (b) (4) (Protocol synopsis included as Appendix C).

**Does the Agency agree that this proposed study satisfies the pediatric requirements for pediatric labeling as part of the 505(b)(2) application?**

**Original FDA Response:**

*Pending.*

**Meeting Comments:** *No additional studies are required for the application.*

**Question 4:** Based on the overwhelming amount of safety and efficacy data of oral ibuprofen in adults and children and the extensive safety and efficacy data of intravenous ibuprofen in (1) 30 febrile adult patients generated by study CPI-CL-006, (2) the safety data in 48 adult normal volunteers generated by studies CPI-CL-001 and CPI-CL-003, 9#) the safety and efficacy data in 231 adult (b) (4) patients, and (4) the safety data from over 500 patients in the literature (presented in Section 9.0) including safe administration of IVib to pre-term infants with PDA, does the Agency agree that the (b) (4) can be initiated upon final agreement of the protocol with FDA?

**Original FDA Response:**

*The purpose of requesting that you the (b) (4) until the results of the adult fever study were available was to obtain PK and safety information upon which to base the target dosage to be studied in hospitalized pediatric population. It is unclear upon what information the proposed dose for the study was based. The requirements for pediatric studies (PK, safety and/or efficacy) are dependent on the information about efficacy and safe dosing in adults.*

We request clarification on the criterion for success in the (b) (4). Is it intended to be a non-inferiority or superiority trial? Is a successful outcome based on the assumption that acetaminophen is considered effective and therefore, any statistically significant difference in the percentage of patients with a temperature reduction from  $\geq 101^{\circ}F$  favoring IVib indicates efficacy?

Meeting Comments:

The Sponsor clarified that the (b) (4). The Sponsor also acknowledged that the literature suggests there might be a difference between the pharmacokinetics of ibuprofen in adults and pediatric patients. The Sponsor suggested that it would be more reliable to base the dose of IV ibuprofen on the oral dose used in pediatric patients than on the adult data. The pediatric dose chosen was based on the approved oral formulation and information in the literature. A dose of 10 mg might be more appropriate than the initially proposed 7.5 mg dose. The PK parameters of oral and IV formulations in adults suggest bioequivalence and no difference between the two formulations was expected in pediatric patients. Furthermore, there have been no safety concerns so far from the adult study. The 16 serious adverse events reported were of unclear etiology, but appeared to be more likely related to the underlying disease in the sick patient population used in the study than study drug.

**Minutes Preparer:** Jane A. Dean, RN, MSN  
**Chair Concurrence:** SHertz  
**Drafted by:** JADean/5-5-04  
**Revised by:** JWitter/5-11-04  
SHertz/5-19-04  
**Initialed by:** CFang/5-13-04  
SHertz/5-19-04  
**Final:** SHertz/5-19-04

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Sharon Hertz

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## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** October 22, 2003  
**TIME:** 4pm  
**LOCATION:** 9201 Corporate Boulevard  
**APPLICATION (DRUG):** IND 62,605 (ibuprofen injection)  
**SPONSOR:** Cumberland Pharmaceuticals  
**TYPE OF MEETING:** Guidance  
**MEETING CHAIR:** Lee Simon, MD  
**MEETING RECORDER:** Ms. Jane A. Dean, RN, MSN

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

| <u>Name of FDA Attendee</u> | <u>Title</u>                | <u>Division Name &amp; HFD#</u> |
|-----------------------------|-----------------------------|---------------------------------|
| 1. Lee S. Simon, MD         | Division Director           | ODEV/DAAODP, HFD-550            |
| 2. Joel Schiffenbauer, MD   | Medical Officer Team Leader | ODEV/DAAODP, HFD-550            |
| 3. Conrad Chen, PhD         | Pharmacology Reviewer       | ODEV/DAAODP, HFD-550            |
| 4. Christina Fang, MD       | Medical Reviewer            | ODEV/DAAODP, HFD-550            |
| 5. Josie Yang, PhD          | Pharm/Tox Team Leader       | ODEV/DAAODP, HFD-550            |
| 6. Abimbola Adebawale, PhD  | Biopharm Reviewer           | OCPB/DPEIII, HFD-880            |
| 7. Tatiana Oussova, MD      | Medical Reviewer            | ODEV/DAAODP, HFD-550            |
| 8. Sue Ching Lin, MS, RPh   | Chemistry Reviewer          | ODEV/DAAODP, HFD-550            |
| 9. Jane A. Dean, RN, MSN    | Project Manager             | ODEV/DAAODP, HFD-550            |

### EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

| <u>External Attendee</u> | <u>Title</u>               | <u>Sponsor/Firm Name</u>   |
|--------------------------|----------------------------|----------------------------|
| 1. Amy Rock, PhD         | Regulatory Affairs         | Cumberland Pharmaceuticals |
| 2. Gordon Bernard, MD    | Medical Director           | Cumberland Pharmaceuticals |
| 3. A. J. Kazimi          | Vice President, Operations | Cumberland Pharmaceuticals |
| 4. Leo Pavliv, RPh       | CEO                        | Cumberland Pharmaceuticals |

**PURPOSE OF THE MEETING:** To gain FDA input and concurrence into the strategy for registration of intravenous ibuprofen for treatment of fever in patients (b) (4)

**MEETING OBJECTIVES:**

1. to obtain FDA input on the current development plan
2. determine if the completed toxicology studies adequately address the FDA's requirements for the NDA
3. obtain FDA agreement that the completed and ongoing clinical trials provide adequate safety and efficacy data for the NDA, assuming the ongoing study also demonstrates that the product is safe and effective.

**QUESTIONS:**

- I. **Development Plan:** In light of the safety and efficacy data from the report entitled (b) (4) and the recently-obtained clinical study CPI-CL-006 (Malaria Report), and safety and efficacy data from the world-wide published literature, does the Division agree that the proposed development plan is appropriate to file a 505(b)(2) NDA?

**Comments from the Division sent to the Sponsor before the meeting:**

*The Sponsor should refer to the meeting minutes for the meetings/teleconference held on February 10 and August 11, 2000, and June 1, 2001 for the study requirements and rationale for obtaining PK, efficacy, and safety data in the target population for the proposed ibuprofen i.v. formulation.*

*Specific requirements will be summarized below:*

1. *Study for (b) (4) indication using carefully selected hospitalized patient populations and use hemodynamically compromised patient populations to obtain information on single-dose dose response and multiple-dose dosing regimen.*
2. *Study single-dose and multiple-dose PK parameters in the target population (including hemodynamically compromised patients) to obtain data about peak after a single dose and peaks at steady states.*
3. *Collect safety data on the Sponsor's product (not from different ibuprofen i.v. formulations) for exposure to 800mg/dose and 3200mg/day for 7 to 10 days in at least 300 patients in the target population.*

At the meeting with the Sponsor, the following were discussed:

### Addendum to Pharmacokinetics

During the meeting the Sponsor asked if the proposed single and multiple dose PK studies either completed or underway were adequate to confirm the PK of single dose and multiple dose regimens. The Agency recommended that the enrollment of both populations (non-critically ill and critically ill) in study 004 should be adequate to determine if there are any differences in the systemic exposure due to the diseases state.

The Sponsor clarified that in the ongoing study 004, of the 30 patients in each of the 3 active treatment arms (100mg, 200mg, and 400mg) 10 are to be selected as critically ill patients, 10 are non-critically ill, and 10 could be from either group. PK sampling for the single-dose and multiple-dose characterization of the IV formulation (including the information about peak level at steady state) will be obtained. PK parameters from the target population will be compared with the data collected from healthy volunteers in study 001, in which the pharmacokinetic parameters were found to be similar between IV and oral formulations.

*FDA Response: The Division considers the proposal acceptable for the antipyretic indication however, adequacy of the data is a review issue.*

### Indication/efficacy

The proposed indication by the Sponsor is "[REDACTED] (b) (4)  
[REDACTED]. The proposed dosage  
"(contingent on results from ongoing efficacy trial)" is "400mg every 4-6  
hours [REDACTED] (b) (4)  
[REDACTED]

*FDA Response: The Division agrees with the Sponsor that there is a need for IV antipyretics. Because the oral formulation of ibuprofen was approved for both analgesic and antipyretic indications at similar dose levels, for a prescription fever indication to stand alone without analgesic indications for the IV formulation there is an anticipated need for presentation and discussion at Advisory Committee meeting. The fever indication needs to be supported by substantial evidence, i.e., replicated positive results obtained from the target population. Due to the concerns of off-label use for not approved indications for an extended period of time the Sponsor needs to provide information on extended-exposure to repeated use for at least a week (refer to safety discussions below for detail). If the longer-term exposure data for the IV formulation are not provided, then the Sponsor needs to propose the mechanisms for restricted distribution/use to limit the drug availability for one-time-use to 2 to 3 days. The Sponsor is recommended to study for analgesic indication as stated in the meeting minutes dated February 10, 2000. Data from analgesic studies may be used for support of multiple-dose safety (for fever indication) and single-dose and multiple-*

dose efficacy for analgesic indication(s).

## **Safety**

The Sponsor clarified that the IV formulation in the (b) (4) whereas the formulation in Cumberland sponsored studies used arginine (b) (4). The two formulations are both of simple solutions which are diluted before IV administration in most of the studies. There was no local irritation reported in the studies using diluted solutions.

*FDA Response:* Because of the known renal toxicity associated with the use of the drug and the safety concerns of hospitalized hemodynamically unstable patients who may receive IV ibuprofen treatment for an extended period, the Division recommended the following to the Sponsor;

- *Exposure in the target population at the maximum recommended dosage for 7 to 10 days using a model that would allow multiple-dose safety to be studied for at least a week;*
- *Stratified enrollment/analysis based on renal impairment status at baseline to obtain more useful information;*
- *Safety studies in high-risk population designed to obtain data to support specific dosing modifications for patients with renal insufficiency of various severities.*

**II. Nonclinical:** With the 28-day dog toxicity studies showing intravenous and oral ibuprofen having the same target organ toxicity, does the Division agree that no additional nonclinical studies will be required for the 505(b)(2) application?

*FDA Response:* No additional animal studies are required for filing an NDA; however, the Sponsor is advised to submit a summary of toxicity information (including the acute toxicity) from the literature for the intravenous ibuprofen and full reports of studies that were conducted with IVIb.

**Minutes Preparer:** Jane A. Dean, RN, MSN  
**Chair Concurrence:** Lee Simon, MD  
**Drafted by:** JADean  
**Initialed by:** LSimon  
**Final:** October 29, 2003

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/s/

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Lee Simon

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