

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201803Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 201803	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Advil Established/Proper Name: ibuprofen sodium Dosage Form: tablet Strengths: 256 mg		
Applicant: Pfizer Consumer Healthcare		
Date of Receipt: July 1, 2010, December 16, 2011 (class 2 response to CR)		
PDUFA Goal Date: June 16, 2012		Action Goal Date (if different):
Proposed Indication(s): Temporarily relieves minor aches and pains due to: headache, toothache, backache, menstrual cramps, the common cold muscular aches, minor pain of arthritis, and temporarily reduces fever.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

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



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

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
OTC NDA 019012 Motrin IB tablet	Clinical safety and efficacy

*each source of information should be listed on separate rows

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

The sponsor conducted a pharmacokinetic study with the proposed sodium ibuprofen dihydrate product and the reference product Motrin IB (ibuprofen) tablet to compare the pharmacokinetic profile. This was done to bridge the safety and efficacy data of the referenced product.

The proposed product is a different salt of the same active ingredient as the reference NDA product (ibuprofen). Clinical PK studies were conducted as part of the Motrin (NDA 019012) submission. The proposed product contains the same dose of active ingredient (ibuprofen) as the referenced product but in a different salt formulation. The previously conducted preclinical studies provide adequate evidence of safety and efficacy. Clinical safety is further supported by substantial post-marketing data of the referenced NDA product: Motrin IB tablet.

RELIANCE ON PUBLISHED LITERATURE

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

YES NO

If “NO,” proceed to question #5.

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

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

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

RELIANCE ON LISTED DRUG(S)

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

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

YES NO
If "NO," proceed to question #10.

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

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Motrin IB tablet	NDA 019012	Y

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

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

N/A YES NO
*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".
 If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

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

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

YES NO
If "YES", please list which drug(s).

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

b) Approved by the DESI process?

YES NO

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

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

c) Described in a monograph?

YES NO

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

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

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES NO

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

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

This application provides for a different salt formulation than the listed drug.

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

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

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

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

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

YES NO

If "NO" to (a) proceed to question #11.

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

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

YES NO

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

YES NO

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

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

Pharmaceutical equivalent(s):

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

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

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

YES NO

If "NO", proceed to question #12.

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

YES NO

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

YES NO

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

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

Pharmaceutical alternative(s):

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

Listed drug/Patent number(s):

No patents listed proceed to question #14

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

YES NO

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

Listed drug/Patent number(s):

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

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

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

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

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

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

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

Date(s):

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

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

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

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

/s/

JAMES C LEE
06/18/2012

2nd Addendum Labeling Review for Advil Tablets and Caplets *Draft Labeling*

SUBMISSION DATES: June 30, 2010, October 13, 2010, February 15, 2011,
March 1, 2011, April 15, 2011, April 22, 2011

NDA/SUBMISSION TYPE: NDA 201-803 (original)

ACTIVE INGREDIENTS: ibuprofen 200 mg (provided as ibuprofen sodium 256 mg)

DOSAGE FORMS: tablets, coated (round tablets and capsule-shaped tablets)

SPONSOR: Pfizer Consumer Healthcare
John Schalago, Director Worldwide Regulatory Strategy
973-660-6809

REVIEWER: Kathleen M. Phelan, R.Ph.

TEAM LEADER: Marina Y. Chang, R.Ph.

I. BACKGROUND

This NDA is for a new ibuprofen salt, ibuprofen sodium 256 mg, which is equivalent to ibuprofen 200 mg.

The April 15, 2011 re-submission is in response to the verbal acceptance of a trade name by DMEPA (review finalized in DARRTS April 27, 2011) and our March 23, 2011 Information Request/Advice letter which conveyed the following recommendations to resolve labeling deficiencies:

- A. Change the established name under the statement of identity from (b) (4) to “Ibuprofen tablets 200 mg (provided as ibuprofen sodium 256 mg)” followed by the pharmacological categories on the outer carton principle display panels (PDPs) of all SKUs, on the side panel that can serve as an alternate PDP of the (b) (4)-count tablet SKU, and on the immediate containers of all SKUs per USP <1121> and 21 CFR 201.61(b).
- B. “Caplet” is not a recognized dosage form designation in the CDER Data Standards manual. Define the term “Caplets” by placing a double asterisk (**) immediately following the word “Caplets” and define the “***” as “***capsule shaped tablets” on the PDPs of all SKUs.

- C. Remove [redacted] ^{(b) (4)} from the PDPs of all SKUs that bear this statement. The phrase may be misconstrued by consumers as a claim about the time to relief of symptoms.
- D. To avoid medication errors, the front panel of the 2-count pouch needs to indicate that each tablet contains 200 mg ibuprofen and that 200 mg is not the total amount of ibuprofen in the pouch. In accordance with 21 CFR 201.62(a), revise the declaration of net quantity of contents statement as follows: 2 coated tablets, 200 mg each.
- E. Wherever the active ingredient is identified in the labeling (on all SKUs), change the active ingredient from [redacted] ^{(b) (4)} to “buprofen 200 mg (provided as ibuprofen sodium 256 mg)” per USP <1121> and 21 CFR 201.66(c)(2).
- F. Change the statement on the 8-count tablets immediate container (vial) from [redacted] ^{(b) (4)} to “Open here to view more product information” or another statement that does not imply the label contains complete Drug Facts.
- G. Provision for the lot/control number (21 CFR 201.17) and expiration date (21 CFR 201.18) on the 2-count immediate container (pouch) must be provided.
- H. Increase the prominence of the peel-back “Lift Here” labels on all the 8-count immediate container (vial) labels. This can be accomplished by increasing the size or changing the font color of the statement so it can be more easily seen. As currently presented, patients and healthcare professionals may not recognize that the required drug facts including important dosing information may be on a peel-back label adhered to the bottle.

The March 23 letter also advised the sponsor to, “Revise the presentation of the proprietary name, when determined and approved, to appear in a contiguous manner including the same font size, type, style, and color type.”

For more complete background and review, see the March 1, and March 17, 2011 labeling reviews.

On April 15, 2011, the sponsor submitted the revised labels listed in the following charts. These are reviewed herein. The labels submitted on April 15, 2011 are compared to the labels submitted on March 1, 2011 if the label was included in the March 1 submission. Labels that were not in the March 1 submission are compared to the labels submitted on February 15, 2011, as noted in the following charts. All labels are compared to the March 23 Information Request/Advice letter.

Capsule-shaped Tablets		
Submitted Labeling	Represented SKUs	Compared to labels submitted on
20-count carton and immediate container (bottle)	none	March 1, 2011
40-count carton and immediate container (bottle)	none	March 1, 2011
80-count carton and immediate container (bottle)	none	March 1, 2011

Round Tablets		
Submitted Labeling	Represented SKUs	Compared to labels submitted on
2-count pouch immediate container	none	Feb 15, 2011
50 x 2-count pouch dispenser outer carton	none	Feb 15, 2011
8-count immediate/outer container (loose vial)	none	Feb 15, 2011
8-count outer container (small blister card with peel-back Drug Facts label)	none	Feb 15, 2011
8-count outer container (long blister card)	none	Feb 15, 2011
8-count immediate container (vial)	none	Feb 15, 2011
20-count carton and immediate container (bottle)	none	Feb 15, 2011 (carton) Mar 1, 2011 (bottle)
40-count carton and immediate container (bottle)	none	Feb 15, 2011 (carton) Mar 1, 2011 (bottle)
80-count carton and immediate container (bottle)	(b) (4)-count	Feb 15, 2011 (carton) Mar 1, 2011 (bottle)
240-count immediate/outer container (bottle)	none	Feb 15, 2011

We e-mailed the sponsor two information requests on April 20, 2011. The first requested re-submission of labeling for the (b) (4) which were included in earlier submissions for NDA 201-803. The sponsor responded that they do not plan to market these SKUs at this time. The second e-mail notified the sponsor that the 2-count pouch submitted on April 15 did not show where the lot number and expiration date would be printed and the 8-count-vial outer container (long hang card) did not have the tamper-evident statement. The sponsor submitted revised 2-count pouch and 8-count-vial outer container (long hang card) labels on April 21 by e-mail and officially on April 22. The labels submitted on April 22 are reviewed in this document.

II. REVIEWER'S COMMENTS

Acceptable

a. General

The trade name has been changed from “Advil (b)(4)” to “Advil.”

b. Outer Carton Label Outside Drug Facts – Principle Display Panel

i. All SKUs

(b)(4) has been changed to “Ibuprofen Tablets 200 mg (provided as ibuprofen sodium 256 mg)” as requested.

The trade name and statement of identity have both been decreased in size. The statement of identity is still one-fourth the height of the trade name.

The color scheme has been changed. Text contrasts with background and remains legible.

ii. 50 x 2-count-pouch dispenser

8-count short, 8-count long hang cards

20-, 40-, 80-count round tablets

240-count outer/immediate container (bottle)

20-, 40-, 80-count capsule-shaped tablets (caplets)

The statement (b)(4) has been removed as requested.

A flag, “NEW”, has been added along with the words, “film-coated ibuprofen sodium.” This is factual, non-promotional, and acceptable.

iii. 20-, 40-, 80-count round tablets

In the net quantity of contents statement, (b)(4) has been changed to “tablets.”

iv. 8-count long hang card

The tamper evident statement was not on the label submitted April 15. The sponsor was notified of the deficiency and it was corrected on the label submitted April 22.

v. 20-, 40-, 80-count capsule-shaped tablets (caplets)

The double asterisk has been added to “caplets” and defined as “**capsule shaped tablets” as requested.

c. Outer Carton Label Outside Drug Facts – Side Panels

i. 50 x 2-count-pouch dispenser

The changes noted above for the Principle Display Panel have been made on the side panels as well as the PDP.

ii. 80-count round tablets

(b) (4) has been changed to “Tablets” in the net quantity of contents statement.

iii. 80-count capsule-shaped tablets (caplets)

The double asterisk has been added to “caplets” and defined as “**capsule shaped tablets” as requested.

iv. 20-count capsule-shaped tablets (caplets)

The tamper-evident statement has been moved from the side panel to the right of the PDP to the side panel to the left of the PDP, just below the last section of Drug Facts. Also, the colors have been changed to match Drug Facts, increasing visibility of the statement.

d. Outer Carton Label Drug Facts

i. All SKUs

Active ingredient

(b) (4) has been changed to “Ibuprofen Tablets 200 mg (provided as ibuprofen sodium 256 mg)” as requested.

ii. 8-count outer/immediate container (loose vial)

“Lift here for more drug facts” has been made more prominent as requested.

e. Immediate Container Label

i. 2-count pouch

(b) (4) has been changed on both the name panel and the **Active ingredient** section to “Ibuprofen Tablets 200 mg (provided as ibuprofen sodium 256 mg)” as requested.

The color scheme of name panel has been changed. The text contrasts with the background and remains legible.

(b) (4) has been changed to “2 Coated Tablets, 200 mg each” as requested.

The location of the expiration date and lot number was not shown on the label submitted April 15. This deficiency was conveyed to the sponsor and the deficiency was corrected on the label submitted April 22.

ii. **8-, 20-, 40-, 80-count round tablets**

20-, 40-, 80-count capsule-shaped tablets (caplets)

(b) (4) has been changed on the front panel to “Ibuprofen Tablets 200 mg (provided as ibuprofen sodium 256 mg)” as requested.

The color scheme of the front panel has been changed. The text contrasts with the background and remains legible.

iii. **8-count vial**

(b) (4) was changed to “Open here to view more product information” as requested. This statement was also increased in size, as requested.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Advil (ibuprofen 200 (provided as ibuprofen sodium 256 mg) coated tablets) labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 2-count immediate container (pouch) and 8-count outer container (long hang card) labeling submitted on April 22, 2011. Also, request that the sponsor submit final printed labeling (FPL) identical to: 2-count-pouch outer container (dispenser), 8-count outer container (short hang card with peel-back drug facts), 8-count outer/immediate container (loose vial), 8-count immediate container (vial), 20-, 40-, and 80-count outer and immediate containers for round tablets and for capsule-shaped tablets (caplets), and 240-count outer/immediate container (bottle) labeling submitted on April 15, 2011.

The sponsor’s submission dated April 15, 2011 notified us that the 80-count round tablet SKU is intended to serve as a representative for the (b) (4) package size. Any changes approved for the 80-count SKU will be incorporated onto the (b) (4) package size.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted on April 15 or April 22, 2011, and evaluated in this labeling review:

Capsule-shaped Tablets (Caplets) Submitted Labeling	Submitted On
20-count carton and immediate container (bottle)	April 15, 2011
40-count carton and immediate container (bottle)	April 15, 2011
80-count carton and immediate container (bottle)	April 15, 2011
Tablets Submitted Labeling	
2-count immediate container (pouch)	April 22, 2011
50 x 2-count-pouch outer carton (dispenser)	April 15, 2011
20-count carton and immediate container (bottle)	April 15, 2011
40-count carton and immediate container (bottle)	April 15, 2011
80-count carton and immediate container (bottle)	April 15, 2011
8-count immediate container (vial)	April 15, 2011
8-count outer carton (short hang card with peel-back Drug Facts label)	April 15, 2011
8-count outer carton (long hand card)	April 22, 2011
8-count outer/immediate container (loose vial)	April 15, 2011
240-count outer/immediate container (bottle)	April 15, 2011

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KATHLEEN M PHELAN
04/27/2011

MARINA Y CHANG
04/27/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 22, 2011

From: Manizheh Siahpoushan, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Through: Zachary Oleszczuk, Pharm.D., Team Leader
Kellie Taylor, Pharm.D., MPH, Associate Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name, Label, and Labeling Review

Drug Name(s), Strength
and Application Advil (Ibuprofen) Tablet, 200 mg
Type/Number: Provided as Ibuprofen Sodium Dihydrate 256 mg
NDA 201803

Applicant: Pfizer Consumer Healthcare

OSE RCM #: 2011-1275, 2011-1276

***** This document contains proprietary and confidential information that should not be released to the public.*****

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EXECUTIVE SUMMARY

This review summarizes DMEPA's evaluation of the proposed proprietary name, Advil for Ibuprofen Tablets provided as Ibuprofen Sodium, and the container label and carton labeling. The proprietary name evaluation did not identify concerns that would render the name unacceptable based on product characteristics and safety profile known at the time of this review. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) finds the proprietary name Advil acceptable for this product.

DMEPA considers this a final name review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, The Division of Nonprescription Clinical Evaluation should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date. Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be re-submitted for review. The conclusions upon re-review are subject to change.

Additionally, our review of the container label and carton labeling for Pfizer Consumer Healthcare's Advil identified several deficiencies. These deficiencies were discussed in labeling meeting and our concerns are addressed with labels and labeling. We have no further comments on the labels and labeling.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from Pfizer Consumer Healthcare on April 15, 2011, for assessment of the proposed proprietary name, Advil, from a safety and promotional perspective. This review also evaluates the container label and carton labeling for Pfizer Consumer Healthcare's Advil for potential to contribute to medication errors.

1.2 REGULATORY HISTORY

Advil is the third proprietary name proposed for this product. The first proprietary name, Advil (b) (4) was found unacceptable in OSE Review # 2010-1537 dated October 8, 2010 because the (b) (4) modifier was found to be fanciful and misleading by DDMAC. The second name, Advil (b) (4) was withdrawn by the Applicant on April 1, 2011.

Additionally, the container labels and carton labeling was previously reviewed in OSE Review # 2011-30, dated March 8, 2011. Label and labeling comments were sent to the Applicant on March 23, 2011. The revisions to the labels and labeling are the subject of this review.

1.3 PRODUCT INFORMATION

Advil is the proposed proprietary name for Ibuprofen 200 mg Tablets provide as Ibuprofen Sodium 256 mg. The new sodium formulation however, has not been proven to have any clinical significance. The recommended dose is one tablet every four to six hours unless otherwise instructed by a healthcare professional; patients should not exceed 6 tablets in 24 hours. Advil will be supplied as 50 packs of 2 coated tablets each, 20-count (tablets and caplets), and 240-count bottles, as well as 8-count vials with child-resistant screw-loc caps. This product will be differentiated from other Advil products by the labels and labeling. The table below details the currently approved and marketed Advil product line.

Drug name*	Active ingredients	Dosing Frequency
Advil	Ibuprofen 200 mg tablets/caplets/gel caps	One (or two) every 4 to 6 hours as needed
Advil Allergy Sinus	Ibuprofen 200 mg Pseudoephedrine HCl 30 mg Chlorpheniramine maleate 2 mg caplets	One caplet every 4 to 6 hours while symptoms persist
Advil Congestion Relief	Ibuprofen 200 mg Phenylephrine HCL 10 mg Tablets	One (or two) tablets every 4 to 6 hours while symptoms persist
Advil Cold and Sinus	Ibuprofen 200 mg Pseudoephedrine HCl 30 mg caplets	One (or two) caplets every 4 to 6 hours while symptoms persist
Advil Liqui-Gels	Solubilized Ibuprofen 200 mg capsules	One (or two) capsules every 4 to 6 hours while symptoms persist
Advil Migraine	Solubilized Ibuprofen 200 mg capsules	Two capsules for migraine (not to exceed 2 capsules in 24 hours)
Advil PM	Ibuprofen 200 mg Diphenhydramine citrate 38 mg caplets	Two caplets at bedtime (not to exceed 2 capsules in 24 hours)
Advil PM Liqui-Gels	Ibuprofen 200 mg Diphenhydramine citrate 25 mg capsules	Two capsules orally at bedtime
Children's Advil	Ibuprofen 100 mg/5 mL suspension Ibuprofen 50 mg tablets	Dosed per weight/age every 6-8 hours if needed
Children's Advil Cold	Ibuprofen 100 mg Pseudoephedrine HCl 15 mg suspension	Dosed per weight/age every 6 hours while symptoms persist
Pediatric Advil	Ibuprofen 100 mg/2.5 mL suspension drops	Dosed per weight/age every 6-8 hours if needed

2 METHODS

The following sections describe the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting the proprietary name, label and labeling risk assessment for the proposed product.

2.1 PROPRIETARY NAME RISK ASSESSMENT

DMEPA considers the active ingredients, dose, dosing frequency of administration, dosage form, route of administration, and indication of use of the proposed product and the currently marketed products that contain the same name, Advil. We also consider the precedence for naming different salt formulations.

2.2 LABEL AND LABELING RISK ASSESSMENT

DMEPA used Failure Mode and Effects Analysis¹ (FMEA), the principles of human factors, and errors learned from the post marketing experience to identify potential sources of error with the proposed product labels and insert labeling. Therefore, we provide recommendations that aim at reducing the risk of medication errors.

Advil will be supplied in different type container closures, which include bottles, pouch, and blister cards. The Applicant submitted the following container label and carton labeling as well as Drug Facts labeling on April 15, 2011 (See Appendix A):

- Pouch 2-count (front and back)
- Pouch Dispenser
- Loose Vial Label 8-count
- Carton and bottle 20-count (tablets and caplets)
- Club bottle 240-count

2.3 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SELECTION OF CASES

Since the Advil product line is currently in the US marketplace, the FDA Adverse Event Reporting System (AERS) was searched for post-marketing safety reports related to medication errors related to the currently marketed Advil product line since these may be indicative of errors that may occur with the introduction of the new product.

The AERS search conducted on January 31, 2011, used the following search terms: MedDRA High Level Group Terms (HLGT): “Medication Errors,” High Level Term (HLT): “Product Label Issues,” and Preferred Term (PT): “Product Quality Issue” along with the Trade Name “Advil” and verbatim term “Advi%.” The period searched was from May 1, 2008 through January 31, 2011. This time frame was used to capture reports occurring after the previous DMEPA search for medication error in OSE Review #2007-2497 dated June 25, 2008.

The reports identified through the FDA Adverse Event Reporting System (AERS) database were manually reviewed to group duplicate reports into cases and to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. For cases describing a medication error, we reviewed the cases to identify factors that contributed to the errors, and to ascertain if these risks might apply to the proposed name, labels and labeling for Advil.

3 RESULTS AND DISCUSSIONS

The proposed proprietary name, Advil, was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. DNCE did not have any objections to the name Advil for this product stated in an email April 14, 2011.

During our review of the proposed proprietary name Advil, DMEPA noted that the proposed product contains the same active ingredient and identical dosing, frequency of administration,

¹ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

route of administration and indication of use to the currently marketed product Advil. Additionally, the dosage form for the proposed products (Film Coated Tablets) is similar to the currently marketed Advil product ((b)(4) Coated Tablet). Thus, the use of the name Advil for this product is appropriate.

Additionally, the salt formulation of this active ingredient is not clinically significant and will not appear as the established name, rather the active moiety, Ibuprofen, will be listed. The only time that a different proprietary name (i.e. root name in conjunction with a modifier) has been used for a product containing a different salt formulation that is not clinically significant is when the different name represents a dosage form (i.e. Advil Liquid Gels for Solubilized Ibuprofen when compared to Advil for Ibuprofen) or a route of administration (i.e. Nexium I.V. Esomeprazole Sodium when compared to Nexium for Esomeprazole Magnesium). Since the currently marketed Advil and the proposed product are administered by the same route of administration (oral) and share the same dosage form (tablets), it is not appropriate to use a different name for this product.

Since this product is the same as the currently marketed Advil except for the active ingredient provided as a different salt formulation and DMEPA has no evidence of name confusion with the name Advil, the proposed name Advil is appropriate for this product.

Additionally, the Applicant proposes to differentiate this product from the currently marketed Advil product with differentiated labels and labeling. DMEPA has evaluated the labels and labeling and finds that they are well differentiated from the Advil products that are currently marketed and we have no further comments.

4 CONCLUSIONS AND RECOMMENDATIONS

Our assessment of the proposed proprietary name indicates that the proposed name, Advil, is appropriate for this product, is not vulnerable to name confusion that could lead to medication errors, nor is the name considered promotional. Thus, DMEPA has no objection to the proposed name, Advil, for this product at this time.

Additionally, DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review or if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change. The Applicant will be notified via letter.

DMEPA finds the labels and labeling for this product acceptable and has no further comments regarding the labels and labeling.

If you have further questions or need clarifications, please contact Cheryle Milburn, project manager, at 301-796-2084.

4.1 COMMENTS TO THE DIVISION

DMEPA finds the labels and labeling for this product acceptable and has no further comments regarding the labels and labeling.

4.2 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Advil, and have concluded that it is acceptable.

Additionally, DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review or if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

If you have further questions or need clarifications, please contact Cherye Milburn, project manager, at 301-796-2084.

5 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***The Document Archiving, Reporting, and Regulatory Tracking System (DARRTS)***

DARRTS is a government database used to track individual submissions and assignments in review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved [brand name](#), [generic drugs](#), [therapeutic biological products](#), [prescription](#) and [over-the-counter](#) human drugs and [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

7. ***Electronic online version of the FDA Orange Book***
(<http://www.fda.gov/cder/ob/default.htm>)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

9. ***Clinical Pharmacology Online*** (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Access Medicine (www.accessmedicine.com)

Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

13. USAN Stems (<http://www.ama-assn.org/ama/pub/category/4782.html>)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

17. LabelDataPlus Database (<http://www.labeldataplus.com/index.php?ns=1>)

LabelDataPlus database covers a total of 36773 drug labels. This includes Human prescription drug labels as well as Active Pharmaceutical Ingredients (APIs), OTC (Application and Monograph) drugs, Homeopathic drugs, Unapproved drugs, and Veterinary drugs.

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/s/

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04/22/2011

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04/22/2011

CAROL A HOLQUIST
04/26/2011

KELLIE A TAYLOR
04/27/2011

**Addendum Labeling Review for
Ibuprofen Tablets 200 mg
provided as Ibuprofen Sodium 256 mg
Draft Labeling
pending proprietary name approval**

SUBMISSION DATES: June 30, 2010, October 13, 2010, February 15, 2011,
March 1, 2011

NDA/SUBMISSION TYPE: NDA 201-803 (original)

ACTIVE INGREDIENTS: ibuprofen 200 mg (provided as ibuprofen sodium 256 mg)

DOSAGE FORMS: tablets, coated (round tablets and capsule-shaped tablets)

SPONSOR: Pfizer Consumer Healthcare
Yael Gozin, Ph.D.
Manager, Global Regulatory Affairs
973-660-5151

REVIEWER: Kathleen M. Phelan, R.Ph.

TEAM LEADER: Marina Y. Chang, R.Ph.

I. BACKGROUND

This NDA is for a new ibuprofen salt, ibuprofen sodium 256 mg, which is equivalent to ibuprofen 200 mg.

This addendum labeling review updates the recommendations made in the March 1, 2011 labeling review. Since that labeling review, further interdisciplinary review team discussion led to a change in the statement of identity. Also, revised labeling was submitted on March 1 that requires some changes to the recommendations.

For a more complete background, see the March 1, 2011 labeling review.

On March 1, 2011, the sponsor submitted the revised labels listed in the following charts. These are reviewed herein.

Capsule-shaped Tablets	
Submitted Labeling	Representative of Following SKUs
20-count carton and immediate container (bottle)	none
40-count carton and immediate container (bottle)	none
80-count carton and immediate container (bottle)	none

Round Tablets	
Submitted Labeling	Representative of Following SKUs
20-count immediate container (bottle)	none
40-count immediate container (bottle)	none
80-count immediate container (bottle)	(b) (4)-count
(b) (4)-count immediate container (bottle)	none
(b) (4)	

The labels submitted on March 1 were compared to the labels submitted on February 15, 2011 and reviewed in the March 1, 2011 labeling review. Only differences between these two submissions are noted in this review. The Recommendations in this review apply to all labels that are specified in each recommendation, although not all labels are reviewed in this addendum review.

II. REVIEWER'S COMMENTS

Acceptable

A. Outer Carton Label Outside Drug Facts – Principle Display Panel

- i. 20-, 40-, and 80-count capsule-shaped tablets**
 - a. In the net quantity of contents, (b) (4) was replaced with “tablets.”
- ii. 40-count capsule-shaped tablets**
 - a. The color scheme of the PDP has been changed to match that of all other SKUs.

B. Immediate Container Label

- i. 20-, 40-, 80-, (b) (4)-count round tablets**
 - a. A picture of the round tablet was added.

- ii. **20-, 40-, and 80-count capsule-shaped tablets**
 - a. In the net quantity of contents, (b) (4) was replaced with “tablets.”
 - b. A picture of the capsule-shaped tablet was added.
- iii. **20-count capsule-shaped tablets**
 - a. The label was changed from a single sheet to a peel-back label with an increase in font size from 4.5 to 6 point.
- iv. **40-count round and capsule-shaped tablets**
 - a. The text was rearranged with a decrease in font size from 5.5 to 4.5 point.
- v. **80-count round and capsule-shaped tablets**
 - a. The text was rearranged with an increase in font size from 4.5 to 5.5 point.

Not Acceptable

A. Outer Carton Label Outside Drug Facts – Principle Display Panel

- i. **All SKUs**
 - a. ***The Statement of Identity***
 - (a) The sponsor changed the established name to “Ibuprofen sodium 256 mg, equivalent to ibuprofen 200 mg,” as requested. However, because clinical reviewers determined that sodium does not contribute to the effect of the drug, the name “ibuprofen sodium” is not in accordance with USP naming conventions (USP33-NF28 Chapter 1121). Therefore, the statement of identity needs to be revised to read
ibuprofen tablets 200 mg
(provided as ibuprofen sodium 256 mg)
Pain reliever/fever reducer (**NSAID**)
- ii. **20-, 40-, and 80-count capsule-shaped tablets**
 - a. ***Dosage form***
 - (a) The sponsor changed (b) (4) in the declaration of net quantity of contents to “tablets.” However, the term “caplets” remains on the PDP. Because caplet is not a USP-recognized dosage form, the sponsor must define the term “Caplets” by placing a double asterisk (**) immediately following the word “Caplets” and define the “**” as “**capsule shaped tablets.”

B. Outer Carton Label Outside Drug Facts – Side and Base panels

- i. **80-count capsule-shaped tablets**
 - Same comment as Not Acceptable A(ii)(a) regarding “Caplets,” above.

C. Outer Carton Drug Facts Label**i. All SKUs****a. Active ingredient/Purpose**

- (a) The sponsor changed the established name to “Ibuprofen sodium 256 mg, equivalent to ibuprofen 200 mg,” as requested. However, because clinical reviewers determined that sodium does not contribute to the effect of the drug, the name “ibuprofen sodium” is not in accordance with USP naming conventions (USP33-NF28 Chapter 1121). Therefore, the statement needs to be revised to read

ibuprofen 200 mg
(provided as ibuprofen sodium 256 mg)

D. Immediate Container Label**i. 20-, 40-, 80-count capsule-shaped tablets****20-, 40-, 80-, (b)(4)-count round tablets**

- a. Same comment as Not Acceptable A(i)(a) regarding the statement of identity, above.

E. General Comment**i. Trade name**

DMEPA rejected the most recently proposed trade name. When a new trade name is approved, the sponsor must re-submit labeling for all SKUs with the new trade name for our review and comment prior to the action due date.

ii Comments from DMEPA’s labeling review of March 8, 2011, discussed at the March 16, 2011 review team’s labeling meeting**a. 2-count pouch**

The pouch front panel needs to indicate that each tablet contains 200 mg ibuprofen and that 200 mg is not the total amount of ibuprofen in the pouch. DMEPA suggested the “presentation of the statement of identity and net quantity should appear as follows on the pouch depending on the final determination of the established name:

Ibuprofen* Tablets 200 mg
Pain Reliever/Fever Reducer (NSAID)
Per Tablet
Two Tablets per pouch
*provided as 256 mg Ibuprofen Sodium”

Based on the labeling meeting discussion and in accordance with 21 CFR 201.61 and 201.62(a), the statement of identity should be the same as comment Not Acceptable A I a (a), above, and the declaration of net quantity of content statement should be revised as “2 coated tablets, 200 mg each” (i.e., add “200 mg each”).

b. 8-count outer / immediate container (loose vial)

DMEPA recommended increasing the prominence of the peel-back statement, “Lift Here” on the label by increasing the font size or changing the font color of the statement so it can be more easily seen. DMEPA noted in their review, “as currently presented, patients and healthcare professionals may not recognize that the required drug facts including important dosing information may be on a peel-back label adhered to the bottle.¹”

III. RECOMMENDATIONS

NOTE: This is a complete list of recommendations, encompassing all labels submitted on February 15, 2011, reviewed in the March 1, 2011, labels submitted on March 1, 2011, reviewed in this document, and recommendations presented by DMEPA at the March 16, 2011, review team labeling meeting.

We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

- Change the established name under the statement of identity from “Ibuprofen sodium 256 mg, equivalent to ibuprofen 200 mg” to “Ibuprofen Tablets 200 mg (provided as ibuprofen sodium (b)(4) immediate containers of all SKUs per USP33-NF28 Chapter 1121 and 21 CFR 201.61(b).
- “Caplet” is not a USP-recognized dosage form. Define the term “Caplets” by placing a double asterisk (**) immediately following the word “Caplets” and define the “**” as “**capsule shaped tablets” on the PDPs of all SKUs.
- Remove (b)(4) from the PDPs of all SKUs that bear this statement. The term (b)(4) cannot be quantified. A different statement with a measurable time and supporting data may be proposed to describe the absorption action.
- To avoid medication errors, the front panel of the 2-count-pouch needs to indicate that each tablet contains 200 mg Ibuprofen and that 200 mg is not the total amount of ibuprofen in the pouch. In accordance with 21 CFR 201.62(a), revise the declaration of net quantity of content statement as follows:
2 coated tablets, 200 mg each
- As currently presented on the 8 count outer / immediate container (loose vial) label patients and healthcare professionals may not recognize that the required drug facts, including important dosing information, is on the peel-back label adhered to the vial. Increase the prominence of the instruction, “LIFT HERE for More Drug Facts.”
- Wherever Active ingredient is listed, either in Drug Facts or other labeling of all SKUs, change the active ingredient from (b)(4) to “Ibuprofen 200 mg (provided as ibuprofen sodium 256 mg)” per USP33-NF28 Chapter 1121 and 21 CFR 201.66(c)(2).

¹ Institute for Safe Medication Practices. Medication Safety Alert. Unrecognized peel-back labels on OTC drugs; January 14, 2010.

- Change the statement on the 8-count tablets immediate container (vial) from (b) (4) to “Open here to view more product information” or another statement that does not imply the label contains complete Drug Facts.
- Provision for the lot/control number (21 CFR 201.17) and expiration date (21 CFR 201.18) on the 2-count pouch must be provided.

Remind the sponsor that when a new trade name is approved by DMEPA, labeling for all SKUs with the approved trade name must be submitted for our review and comment and approval prior to the action due date.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted on March 1, 2011, and evaluated in this labeling review:

Capsule-shaped Tablets Submitted Labeling
20-count carton and immediate container (bottle)
40-count carton and immediate container (bottle)
80-count carton and immediate container (bottle)
Round Tablets Submitted Labeling
20-count immediate container (bottle)
40-count immediate container (bottle)
80-count immediate container (bottle)
(b) (4)-count immediate container (bottle)
(b) (4)

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KATHLEEN M PHELAN
03/17/2011

MARINA Y CHANG
03/17/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 8, 2011

To: Andrea Leonard-Segal, M.D., M.S., Director
Division of Nonprescription Clinical Evaluation

Through: Zachary Oleszczuk, Pharm.D., Team Leader
Kellie Taylor, PharmD., MPH, Associate Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

From: Manizheh Siahpoushan, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s) and Application Type/Number: Advil (b) (4) (Ibuprofen Sodium) Tablets
Ibuprofen 200 mg
Provided as 256 mg Ibuprofen Sodium Dihydrate

NDA 201803

Applicant: Pfizer Consumer Healthcare

OSE RCM #: 2011-30

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1 INTRODUCTION

This review evaluates the container label and carton labeling for Pfizer Consumer Healthcare's Advil (b)(4) for their potential to contribute to medication errors. The container labels and carton labeling were submitted for review on February 15, 2011 and March 1, 2011.

1.1 REGULATORY HISTORY

On December 31, 2010, the Applicant submitted a request for proprietary name review for Advil (b)(4) after DMEPA found the first proposed proprietary name, Advil (b)(4) unacceptable on October 8, 2010. Additionally, on February 15, 2011 and March 1, 2011 the Applicant submitted container labels and carton labeling for the following: a 2-count pouch and a 50-count pouch dispenser, an 8-count loose vial, blister cards (8-count, 20-count, 24-count), 20-count, 40-count, and 80-count bottles and cartons (for both tablets and caplets), (b)(4)-count bottle and carton (b)(4) and a 240-count club bottle.

2 METHODS

Since the Advil product line is currently in the US marketplace, the FDA Adverse Event Reporting System (AERS) was searched for post-marketing safety reports related to these products that could potentially cause confusion with the introduction of "Advil (b)(4)".

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SELECTION OF CASES

The AERS search conducted on January 31, 2011, used the following search terms: MedDRA High Level Group Terms (HLGT): "Medication Errors," High Level Term (HLT): "Product Label Issues," and Preferred Term (PT): "Product Quality Issue" along with the Trade Name "Advil" and verbatim term "Advi%." The period searched was from May 1, 2008 through January 31, 2011. This time frame was used to capture reports from the previous DMEPA search for medication error in OSE Review #2007-2497 dated June 25, 2008.

The reports identified through the FDA Adverse Event Reporting System (AERS) database were manually reviewed to group duplicate reports into cases and to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. For cases describing a medication error, we reviewed the cases to identify factors that contributed to the errors, and to ascertain if these risks might apply to the proposed labels and labeling to Advil (b)(4). After eliminating reports not relevant to medication errors occurring with Advil such as adverse events, allergic reaction, accidental exposure, concomitant treatment, suicide attempt, chewing the tablet, and lack of pain relief, seven cases remained.

2.2 LABELS AND LABELING RISK ASSESSMENT

DMEPA used Failure Mode and Effects Analysis¹ (FMEA), the principles of human factors, and errors learned from the post marketing experience to identify potential sources of error with the proposed product labels and insert labeling. Therefore, we provide recommendations that aim at reducing the risk of medication errors.

¹ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Advil (b) (4) will be supplied in different type container closures, which include bottles, pouch, and blister cards. The Applicant submitted the following container label and carton labeling as well as Drug Facts labeling on February 15, 2011 and March 1, 2011 (See Appendices A and B):



3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

DMEPA retrieved a total of fourteen reports (n=14) from the FDA Adverse Event Reporting System (AERS) database associated with the currently marketed Advil product line. After eliminating cases not relevant to medication errors occurring with Advil as described in section 2.1, seven cases remained. All cases are from France and involve pediatric overdosage or wrong frequency of administration, (i.e. every 3 to 4 hours instead of every 6 to 8 hours) with ibuprofen suspension. The cases did not provide enough details to determine the root cause of the errors. For a list of the ISR numbers see Appendix C.

3.2 LABELS AND LABELING

Our evaluation of labels and labeling identified the following deficiencies:

- The entire proprietary name is not presented in a consistent manner.
- The number of tablets in each pouch is not in agreement with the dosing recommendation of 1 to 2 tablets.
- The peel-back “Lift Here” label for the 8-count vial may be overlooked.
- The statement of identity does not contain the dosage form.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation identified areas where information on the container labels and carton labeling can be improved to minimize medication errors or confusion. Section 4.1 *Comments to the Division* and section 4.2 *Comments to the Applicant*, contain our recommendations for the container labels and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact OSE Regulatory Project Manager Cherye Milburn at 301-796-2084.

4.1 COMMENTS TO THE DIVISION

DMEPA recommends that each pouch contain only one tablet. Currently, each pouch contains two tablets and is incongruent with the recommended dose of “one to two tablets every 4 to 6 hours.” Additionally, patients may misinterpret the current presentation of the strength to mean that 200 mg is the total content of the pouch and not per tablet.

4.2 COMMENTS TO THE APPLICANT

A. All Container and Carton Labeling

We recommend revising the presentation of the proprietary name to appear in a contiguous manner including the same font size, type, style, and color type. This presentation will emphasize the full name of the product. As currently presented, the name modifier, (b)(4) may be overlooked leading to confusion with other Advil products.

B. Pouch Container Front Label

Revise the net quantity to indicate that each tablet contains 200 mg Ibuprofen and that the 200 mg is not the total amount of the two tablets. The presentation of the statement of identity and net quantity should appear as follows on the pouch depending on the final determination of the established name:

Ibuprofen* Tablets 200 mg
Pain Reliever/Fever Reducer (NSAID)
Per Tablet
Two Tablets per pouch
*provided as 256 mg Ibuprofen Sodium

C. Container Labels For the 8-count Vial

We recommend increasing the prominence of the peel- back “Lift Here” labels on all the container labels for the 8-count vial. This can be accomplished by increasing the size or changing the font color of the statement so it can be more easily seen. As currently presented, patients and healthcare professionals may not recognize that the required drug facts including important dosing information may be on a peel-back label adhered to the bottle.²

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² Institute for Safe Medication Practices. Medication Safety Alert. Unrecognized peel-back labels on OTC drugs; January 14, 2010.

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03/08/2011

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03/08/2011

KELLIE A TAYLOR
03/08/2011

CAROL A HOLQUIST
03/08/2011

**Labeling Review for
Ibuprofen Tablets 200 mg
provided as Ibuprofen Sodium 256 mg
Draft Labeling
pending proprietary name approval**

SUBMISSION DATES: June 30, 2010, October 13, 2010, February 15, 2011

NDA/SUBMISSION TYPE: NDA 201-803 (original)

ACTIVE INGREDIENTS: ibuprofen 200 mg, provided as ibuprofen sodium 256 mg

DOSAGE FORMS: tablets, coated (round tablets and capsule-shaped tablets)

SPONSOR: Pfizer Consumer Healthcare
Yael Gozin, Ph.D.
Manager, Global Regulatory Affairs
973-660-5151

REVIEWER: Kathleen M. Phelan, R.Ph.

TEAM LEADER: Marina Y. Chang, R.Ph.

I. BACKGROUND

This NDA is for a new ibuprofen salt, ibuprofen sodium 256 mg, which is equivalent to ibuprofen 200 mg.

This is our preliminary labeling review. If safety-related information becomes available prior to the final approval, further labeling revisions may be required.

The following requests were sent to the sponsor on September 13 based on the filing review:

- Submit (b) (4)-count tablets immediate container (bottle) label for review and comment.
- Submit annotated specifications for the Drug Facts labels for all SKUs in accordance with 201.66(d).

The (b) (4)-count tablets immediate container (bottle) label and annotated specifications were submitted by the sponsor on October 13, 2010.

Following the initial team meeting on September 20, the sponsor was asked to clarify what SKUs are to be marketed. This is because the chemistry section of the NDA lists three container sizes,

(b) (4)-count, that are not included or represented by the submitted labels. In a letter dated February 11, 2011, the sponsor clarified that these three sizes are not to be marketed at this time.

On February 15, the sponsor submitted a complete set of revised labels. These are reviewed herein.

Capsule-shaped Tablets	
Submitted Labeling	Representative of Following SKUs
20-count carton and immediate container (bottle)	none
40-count carton and immediate container (bottle)	none
80-count carton and immediate container (bottle)	none

Round Tablets	
Submitted Labeling	Representative of Following SKUs
2-count pouch	none
50 x 2-count pouch dispenser	none
8-count-vial outer container (short hang card with peel-back Drug Facts label (piggyback))	none
8-count-vial outer container (long hang card)	none
3 x 8-count-vial outer container (hang card)	none
8-count immediate container (vial)	none
8-count outer / immediate container (loose vial)	none
20-count carton and immediate container (bottle)	none
40-count carton and immediate container (bottle)	none
80-count carton and immediate container (bottle)	(b) (4)-count
(b) (4) count carton and immediate container (bottle) (b) (4)	none
240-count outer / immediate container (bottle)	none

The proposed Drug Facts labels were compared for content to the currently approved Drug Facts label for Advil Tablets (b) (4)-count outer / immediate container (bottle), which was approved as part of NDA 18-989/S-80 on September 1, 2010.

II. REVIEWER'S COMMENTS

Acceptable

A. General

i. All SKUs

The Chemistry review finalized on February 28, 2011 states:

FDA Comment: The descriptor “caplet” is not listed in the USP as a recognized dosage type. We have reviewed your proposal and found that there is no compelling new dosage form technology to support creation of the new dosage form name “caplet”. Replace the descriptor “caplet” with the USP recognized descriptor “tablet” in all labeling and packaging. Pfizer is in the process of removing the word “caplet” from the proposed labeling; this will be confirmed during the labeling review.

ODE IV has accepted the term caplet, with an asterisk that defines caplet as “capsule-shaped tablet,” for many OTC products, including other Advil products. If we deny the term caplet for this application, it will establish a new policy and the agency would need to send information request letters to all sponsors who have approved labeling with the term caplets asking them to revise the labeling to the appropriate USP recognized term.

Currently, DNRD agrees that the term caplet cannot be used as an official dosage form in the established name as part of the statement of identity.

No additional labeling changes were recommended in the Clinical Review or in the Pharmacokinetic review of the application.

B. Outer Carton Label Outside Drug Facts – Principle Display Panel

i.



required on the PDP, including the boxed statement, “This package for households without young children.”

C. Outer Carton Drug Facts Label

i. All SKUs

a. Inactive ingredients

The inactive ingredients were discussed with ONDQA and the listing is acceptable.

Ingredient from NDA	How ingredient appears on label
Acesulfame Potassium	(b) (4)
(b) (4)	
(b) (4)	
Carnauba Wax	
Colloidal Silicon Dioxide	
(b) (4)	
Mannitol	
Microcrystalline Cellulose	
(b) (4)	
(b) (4)	
Sodium Lauryl Sulfate	
Sucralose	

* essentially removed during processing

b. Other information

The sodium content in each dosage unit is provided in accordance with 21 CFR 201.64. The molecular formula for the drug substance indicates that there is one sodium atom associated with each active ingredient molecule. Sodium ibuprofen dihydrate has a molecular weight of 264.29 g/mole and sodium has a molecular weight of (b) (4) g/mole. As such, the amount of sodium per 256 mg sodium ibuprofen dosage form is correctly labeled as 22 mg.

c. Other Sections/Issues

The Drug Facts labels meet format specifications as stated in 21 CFR 201.66(c) and (d). The labels for the 20- and 40-count round tablets and the 20- and 40-count capsule-shaped tablets are in accordance with 21 CFR 201.66(d)(10).

D. Immediate Container Label**i. All SKUs****a. Other information**

Same comment as C(i)(b) regarding sodium content, above.

ii. 2-count pouch**a. Declaration of Net Quantity of Contents statement**

On the label submitted on June 30, 2010, the declaration of net quantity of contents statement was not separated from the statement of identity per 21 CFR 201.62. This deficiency was conveyed to the sponsor and the deficiency is corrected on the label submitted on February 15, 2011.

**iii. 20-, 40-, 80-count capsule-shaped tablets
8-count tablets immediate container (vial)
20-, 40-, 80-, (b)(4)-count round tablets****a. Stomach Bleeding Warning**

The stomach bleeding warning begins, (b)(4)
(b)(4) According to 21 CFR 201.326(a)(2)(iii)(A), the phrase should read, "This product contains an NSAID..." Because NSAID is not defined elsewhere on the immediate container, this addition adds valuable information.

On the labels submitted on June 30, 2010, the bolded subheading, **Stomach bleeding warning:**, was not present as required in 21 CFR 201.326(a)(2)(iii)(A). This deficiency was conveyed to the sponsor and the deficiency is corrected on the labels submitted on February 15, 2011.

Not Acceptable**A. Outer Carton Label Outside Drug Facts – Principle Display Panel****i. All SKUs****a. The Statement of Identity**

(a) This statement needs to be revised in accordance with 21 CFR 201.61(b) as follows

ibuprofen tablets 200 mg
(provided as 256 mg ibuprofen sodium)
Pain reliever/fever reducer (**NSAID**)

(b) We will reserve additional comment on the format of the proprietary name in relation to the Statement of Identity until the Division of Medication Error and

Prevention Analysis (DMEPA) has notified the sponsor of an acceptable proprietary name.

b. *The declaration of net quantity of contents statement*

- (a) Because “caplet” is not a USP officially recognized dosage form, the sponsor must define the term “Caplets” by placing an asterisk immediately following the word “Caplets” and define the asterisk as “ * capsule shaped tablet”.

ii. 20-, 40-, 80-count capsule-shaped tablets

50 x 2-count-pouch tablets dispenser

8-count-vial tablets outer container with peel-back Drug Facts (short hang card)

8-count-vial tablets outer container (long hang card)

3 x 8-count-vial tablets outer container (hang card)

20-, 40-, 80-, (b) (4)-count round tablets

240-count tablets outer / immediate container (bottle)

a. (b) (4) *promotional statement*

This statement should be removed. The agency discourages the use of the term (b) (4) because it can not be quantified. The sponsor should be advised to use a statement with a measurable time that is supported by data.

iii. (b) (4)-count tablets

a. *Alternate Principle Display Panel*

Same comment as Not Acceptable A(i)(a) regarding statement of identity, above.

iv. 40-count capsule-shaped tablets

b. *Principle Display Panel Background*

The background of the PDP is white with blue lines. The statement of identity is in white text with gray outlines. The contrast between text and background is insufficient to make the statement of identity “prominent and conspicuous” as required in 21 CFR 201.61. The sponsor must change the color scheme to make the statement of identity more prominent.

B. Outer Carton Label Outside Drug Facts – Side and Base panels

i. 50 x 2-count-pouch tablets dispenser

Same comment as Not Acceptable A(ii)(a) regarding (b) (4) above.

C. Outer Carton Drug Facts Label**i. All SKUs****a. Active ingredient/Purpose**

Revise the Active ingredient from [REDACTED] (b) (4) to “Ibuprofen 200 mg (provided as ibuprofen sodium 256 mg).”

D. Immediate Container Label**i. 20-, 40-, 80-count capsule-shaped tablets
8-count tablets immediate container (vial)
20-, 40-, 80-, [REDACTED] (b) (4)-count round tablets
2-count-pouch tablets**

a. Same comment as Not Acceptable A(i)(a) regarding the established name under the statement of identity, above.

ii. 8-count tablets immediate container (vial)

a. The statement directing the consumer to unroll the label for more information says, [REDACTED] (b) (4) Complete Drug Facts are not on this label, so this statement is misleading. It should be changed to a more correct statement, such as, “Open here for more product information” or other similar language.

2-count-pouch tablets

- a. Same comment as Not Acceptable C(i)(a) regarding the listing of the Active ingredient, above.
- b. Provision for the lot number (21 CFR 201.17) and expiration date (21 CFR 201.18) must be provided.

III. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

- Change the listing of the established name under the statement of identity from [REDACTED]^{(b)(4)} to “Ibuprofen Tablets 200 mg (provided as ibuprofen sodium 256 mg)” followed by the pharmacological categories on the outer carton principle display panels (PDPs) of all SKUs, on the side panel that can serve as an alternate PDP of the [REDACTED]^{(b)(4)}-count tablet SKU, and on the immediate containers of all SKUs per USP33-NF28 S2 Reissue Chapter 1121.
- “Caplet” is not a USP officially recognized dosage form. Define the term “Caplets” by placing an asterisk immediately following the word “Caplets” and define the asterisk as “*capsule shaped tablet” in the declaration of net quantity of contents statement for all SKUs.
- Wherever Active ingredient is listed, either in Drug Facts or other labeling of all SKUs, change the listing of the active ingredient from [REDACTED]^{(b)(4)} to “Ibuprofen 200 mg (provided as ibuprofen sodium 256 mg)” per USP33-NF28 S2 Reissue Chapter 1121.
- Remove [REDACTED]^{(b)(4)} from the PDPs of all SKUs that bear this statement. The term [REDACTED]^{(b)(4)} cannot be quantified. A different statement with a measurable time and supporting data may be proposed to describe the absorption action.
- Change the statement on the 8-count tablets immediate container (vial) from [REDACTED]^{(b)(4)} to “Open here to view more product information” or another statement that does not imply the label contains complete Drug Facts.
- Change the color scheme of the 40-count capsule-shaped tablets outer container to make the statement of identity “prominent and conspicuous” as required in 21 CFR 201.61.
- Provision for the lot/control number (21 CFR 201.17) and expiration date (21 CFR 201.18) on the 2-count pouch must be provided.

Inform the sponsor that these are preliminary labeling comments. If safety-related information becomes available prior to the final approval, further labeling revisions may be required. Also, this review does not address the acceptability of the proprietary name. The acceptability of the proprietary name is pending DMEPA’s review, comment, and approval.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted on February 15, 2011, and evaluated in this labeling review:

Capsule-shaped Tablets Submitted Labeling
20-count carton and immediate container (bottle)
40-count carton and immediate container (bottle)
80-count carton and immediate container (bottle)
Round Tablets Submitted Labeling
2-count pouch
50 x 2-count pouch dispenser
8-count-vial outer container (short hang card with peel-back Drug Facts label (piggyback))
8-count-vial outer container (long hang card)
3 x 8-count-vial outer container (hang card)
8-count immediate container (vial)
8-count outer / immediate container (loose vial)
20-count carton and immediate container (bottle)
40-count carton and immediate container (bottle)
80-count carton and immediate container (bottle)
(b) (4) -count carton and immediate container (bottle) (b) (4)
240-count outer / immediate container (bottle)

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KATHLEEN M PHELAN
03/01/2011

MARINA Y CHANG
03/01/2011

MEMORANDUM

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

DATE: January 18, 2011

TO: Andrea Leonard Segal, M.D.
Director, Division of Nonprescription Clinical
Evaluation (DNCE)

FROM: Abhijit Raha, Ph.D., Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 1/25/11*
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 201-803, Advil (b)(4)
(Ibuprofen sodium) Tablets, 256 mg, Sponsored by
Pfizer Consumer Healthcare

At the request of DNCE, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study Number: AH-09-08

Study Title: "A Pharmacokinetic Study Comparing Sodium
Ibuprofen Tablets to Ibuprofen Liquigels
and Tablets"

The audits of the clinical and analytical portions of study AH-09-08 were conducted at PPD Development, LP, Austin, TX and (b)(4) respectively.

Clinical Site: PPD, Inc., Austin, TX (FEI Number:
3003813358)

Following inspection of the clinical site (Dec 16, 17, 20 of 2010), Form FDA-483 was not issued, and no significant clinical findings were noted.

Analytical Site: (b)(4)

Page 2 - NDA 201-803, Advil (b)(4) (Ibuprofen sodium)
Tablets, 256 mg

Following inspection at the analytical site (December 6-9, 2010), a one-item Form FDA-483 was issued (**Attachment 1**). DSI received the written response (dated December 20, 2010) from (b)(4) on December 22, 2010 (**Attachment 2**). Our evaluation of the Form FDA-483 observation (**in bold type**), and the firm's response to the observation follow.

1. **The ibuprofen LC/MS/MS assay was not fully validated in that the effect of contraceptives on assay precision and accuracy was not evaluated as about 10% of study subjects were taking different pairs of contraceptives. Furthermore, the firm's Standard Operating Procedure (SOP) LP-BA-009 entitled, "Determination of Non-Interference of Concomitantly Administered Compounds", concerning performance of analyte interference testing with concomitant medications was not followed.**

In their response, (b)(4) acknowledged the above observation in that there was an absence of testing for potential interference from contraceptives. Following the inspection, (b)(4) conducted interference tests on the contraceptives used by subjects in study AH-09-08, which were levonorgestrel, ethinyl estradiol, norethindrone, and ethynodiol diacetate. No analyte interference was observed (Validation Report Addendum 7, LCMSB 409, **Attachment 3**). Furthermore, the firm will revise their method validation SOP to include routinely analyte interference testing for three of the most commonly used contraceptives, ethinyl estradiol, levonorgestrel, and norethindrone.

Conclusion:

Following the inspections at the clinical and analytical study sites and after evaluating the response to the 483 observations submitted by (b)(4), DSI recommends that the data from study AH-09-08 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.


Abhijit Raha, Ph.D.

Page 3 - NDA 201-803, Advil (b)(4) (Ibuprofen sodium)
Tablets, 256 mg

Final Classification:

**PPD, Inc., Austin, TX (Clinical)-NAI
(FEI Number: 3003813358)**

(b)(4)

cc: DARRTS

CDER DSI PM TRACK

OND/ODE IV/DNCE/Andrea Segal, James Lee (HFD-560)

HFD-48/Ball/Haidar/Yau/Dejernett/Raha/CF

HFR-CE2545/Dianne H. Milazzo

HFR-CE250/Cynthia A. Harris (BIMO)

HFR-CE250/Christine Smith (DIB), Evelyn Bonnin (DD)

Draft: AR 1/18/2011

Edit:

DSI: (b)(4); O:\BE\EIRCover\201803.(b)(4).ibu.doc

FACTS (b)(4) 6

ATTACHMENTS

1. Form FDA-483 for Study AH-09-08
2. (b)(4) Response to Form FDA-483 Observation
3. Interference Evaluations for Method for Determination of Ibuprofen in Human Plasma by LC/MS/MS

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/s/

ABHIJIT RAHA

01/25/2011

Dr. Martin Yau, Acting Team Leader of the Bioequivalence Program, signed the original paper copy of this document on January 25, 2011.

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information	
NDA # 201803 BLA#	NDA Supplement #:S- BLA STN #
Efficacy Supplement Type SE-	
Proprietary Name: Advil ^{(b)(4)} Established/Proper Name: Ibuprofen sodium Dosage Form: tablet Strengths: 256 mg	
Applicant: Pfizer Consumer Healthcare Agent for Applicant (if applicable):	
Date of Application: July 1, 2010 Date of Receipt: July 1, 2010 Date clock started after UN:	
PDUFA Goal Date: May 1, 2011	Action Goal Date (if different):
Filing Date: August 30, 2010	Date of Filing Meeting: August 4, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 2	
Proposed indication(s)/Proposed change(s): Pain reliever, fever reducer	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input checked="" type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 105341				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

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

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

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

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

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

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

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

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

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

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 4, 2010

BLA/NDA/Supp #: 201803

PROPRIETARY NAME: Advil (b) (4)

ESTABLISHED/PROPER NAME: sodium ibuprofen dihydrate

DOSAGE FORM/STRENGTH: 256 mg tablet

APPLICANT: Pfizer Consumer Healthcare

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Pain reliever, Fever reducer

BACKGROUND: Pfizer Consumer Healthcare has submitted a 505(b)(2) NDA for a new 256 mg sodium ibuprofen dihydrate tablet formulation. This product would be marketed under the proposed tradename Advil (b) (4). Reference is made to OTC Motrin (ibuprofen) tablet, 200 mg (NDA 19-012), Advil Liqui-Gels (ibuprofen) capsules, 200 mg (NDA 20-402), and Advil (ibuprofen) tablets, 200 mg (NDA 18-989) for clinical safety and efficacy. A Pre-NDA meeting was held with Pfizer on December 15, 2009 to discuss the appropriate reference listed drug and the content of the NDA submission.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	James Lee	Y
	CPMS/TL:	Melissa Furness	Y
Cross-Discipline Team Leader (CDTL)	Lesley Furlong		Y
Clinical	Reviewer:	Priscilla Callahan-Lyon	Y
	TL:	Lesley Furlong	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:	Kate Phelan	Y
	TL:	Marina Chang	Y

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Suresh Doddapaneni	
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Cindy Li	Y
	TL:	Wafa Harrouk	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	John Hill	Y
	TL:	Swapan De	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Cathy Miller	Y
	TL:	Zachary Oleszczuk	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

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

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

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

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

Appendix A (NDA and NDA Supplements only)

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

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

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

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/s/

JAMES C LEE
09/17/2010

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: September 2, 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: David Lee, Ph.D., Clinical Pharmacology Reviewer
Suresh Doddapaneni, Ph.D., Director

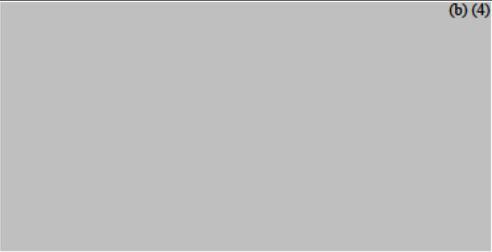
Director, Division of Pharmaceutical Evaluation, HFD-###

FROM: James Lee, Regulatory Project Manager, Division of Nonprescription Clinical Evaluation, HFD-560

SUBJECT: Request for Biopharmaceutical Inspections
NDA 201803
Advil ^{(b) (4)} (Ibuprofen sodium) tablet, 256 mg
Pfizer Consumer Healthcare

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
AH-09-08	PPD Development, LP 7551 Metro Center Drive Suite 200 Austin, Texas 78744 512-447-2985 Investigator: Aziz L. Laurent, MD	 (b) (4)

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International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **INSPECTION SUMMARY GOAL DATE**. We intend to issue an action letter on this application by **ACTION GOAL DATE**.

Should you require any additional information, please contact James Lee, Regulatory Project Manager, 301-796-5283.

Concurrence: (Optional)

Name Medical Team Leader Biopharm Team Leader

Name Medical Reviewer Biopharm Reviewer

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/s/

JAMES C LEE
09/24/2010

Filing Review for Advil ^{(b) (4)} Tablets and Caplets

SUBMISSION DATES: June 30, 2010

NDA/SUBMISSION TYPE: NDA 201-803 (original)

ACTIVE INGREDIENTS: 256 mg sodium ibuprofen dihydrate (200 mg ibuprofen)

DOSAGE FORMS: tablets, coated (Tablets and Caplets [capsule-shaped tablets])

SPONSOR: Pfizer Consumer Healthcare
Yael Gozin, Ph.D., Manager, Global Regulatory Affairs
973-660-5151

REVIEWER: Kathleen M. Phelan, R.Ph.

TEAM LEADER: Marina Y. Chang, R.Ph.

Tablets	
Submitted Labeling	Representative of Following SKUs
2-count pouch	none
50 x 2-count pouch dispenser	none
loose vial	none
8-count vial small blister card and piggyback	none
8-count vial long blister card	none
3 x 8-count vial blister card	none
8-count immediate container (vial)	none
20-count carton and immediate container (bottle)	none
40-count carton	80, ^{(b) (4)} -count carton
40-count immediate container (bottle)	80-, ^{(b) (4)} -count immediate containers (bottles)
^{(b) (4)} -count carton ^{(b) (4)}	
240-count immediate container (bottle)	

Caplets	
Submitted Labeling	Representative of Following SKUs
20-count carton and immediate container (bottle)	none
80-count carton and immediate container (bottle)	none

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	Yes	original NDA
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	No	
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	No	(b) (4)
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	No	Need to request annotated specifications for all SKUs.
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include “prescription strength” or similar statements?	Yes	Strength on PDP is 256 mg because of the salt form. Statement on PDP: <div style="background-color: #cccccc; width: 100px; height: 1em; margin-top: 5px;">(b) (4)</div>
Do any of the labels include “#1 doctor recommended” or similar endorsement statements?	Yes	(b) (4)
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes	
Does a medical officer need to review any clinical issues?	Yes	Original NDA.
If SLR, should ONDQA also review?	n/a	

Information Request:

Information request is necessary.

Submit (b)(4)-count Tablets immediate container (bottle) label for review and comment.

Submit annotated specifications for the Drug Facts labels for all SKUs.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201803	ORIG-1	PFIZER CONSUMER HEALTHCARE	Sodium Ibuprofen, 256 mg (ibuprofen 200 mg)

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/s/

KATHLEEN M PHELAN
08/04/2010

MARINA Y CHANG
08/05/2010