

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205352Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

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

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

NDA NUMBER

205352

NAME OF APPLICANT/NDA HOLDER

Bayer HealthCare LLC
Consumer Care Division

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

TRADE NAME (OR PROPOSED TRADE NAME)

Aleve PM

ACTIVE INGREDIENT(S)

naproxen sodium
diphenhydramine hydrochloride

STRENGTH(S)

220 mg per tablet
25 mg per tablet

DOSAGE FORM

tablet, oral

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

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

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

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

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

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

5. No Relevant Patents

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

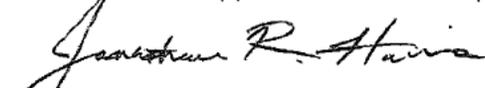
6. Declaration Certification

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

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

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

Date Signed



4 Jan 2013

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

Check applicable box and provide information below.

NDA Applicant/Holder

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

Patent Owner

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

Name

Jonathan R. Harris

Address

555 White Plains Road

City/State

Tarrytown, NY

ZIP Code

10591

Telephone Number

(914) 333-6168

FAX Number (if available)

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E-Mail Address (if available)

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

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

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

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Patent Certification [505(b)(2) only]

Bayer HealthCare



PATENT CERTIFICATION

Applicant, Bayer HealthCare LLC, certifies pursuant to 21 U.S.C. § 355(b)(2)(A)(i) (Section 505(b)(2)(A)(i) of the FD&C Act) that, to the best of its knowledge, no patent information has been filed which claims the drug, or a use thereof, for which Applicant is seeking approval, for investigations not conducted by Applicant and for which a right of reference has not been obtained.

Patents & Licensing

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Respectfully submitted,

Bayer HealthCare LLC

A handwritten signature in cursive script that reads "Jonathan R. Harris".

Jonathan R. Harris
Patent Counsel

EXCLUSIVITY SUMMARY

NDA # 205352

SUPPL #

HFD # 560

Trade Name Aleve PM

Generic Name naproxen 220 mg, diphenhydramine 25 mg

Applicant Name Bayer Healthcare

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 20204 Aleve (naproxen sodium) tablets

NDA# 21076 Aleve Cold/Sinus (naproxen sodium, 220 mg / PSE)

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Investigation #1: Study 14837 (pivotal efficacy and safety study to determine the safe and effective dose for naproxen sodium/diphenhydramine combination product)

Investigation #2: Study 15881 (second, supportive, pivotal efficacy and safety study)

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

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

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

Investigation #1: Study 14837 YES NO

Investigation #2: Study 15881 YES NO

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

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

Investigation #1: Study 14837 YES NO

Investigation #2: Study 15881 YES NO

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

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

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

YES NO

If yes, explain:

=====

Name of person completing form: Jade Pham
Title: Regulatory Project Manager
Date: 1/7/14

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

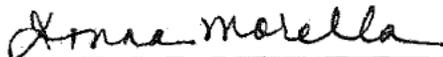
/s/

JADE A PHAM
01/09/2014

THERESA M MICHELE
01/11/2014

1.3.3 Debarment Certification

Bayer HealthCare Consumer Care 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 new drug application for naproxen sodium plus diphenhydramine hydrochloride tablets.



Donna Morella, LCSW, CCRA

04 Jan 2013
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205352 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Aleve PM Established/Proper Name: naproxen 220 mg/ diphenhydramine 25 mg Dosage Form: tablet		Applicant: Bayer Healthcare Agent for Applicant (if applicable):
RPM: Jade Pham		Division: Division of Nonprescription Clinical Evaluation
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(For additional information regarding 505(b)(2)s, please refer to http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s): diphenhydramine</p> <p>Provide a brief explanation of how this product is different from the listed drug. This drug contains a combination of naproxen and diphenhydramine.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input checked="" type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>January 20, 2014</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None

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

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

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 4</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input checked="" type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

❖ Copy of this Action Package Checklist ⁴	1/22/14
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Officer/Employee List

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

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 1/17/14
---	-------------------------------

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	

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

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	1/9/14
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Acceptability letter: 6/24/13 Prop Name Review: 6/21/13 Promotional Review: 6/30/13
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 9/26/13 <input type="checkbox"/> DMPP/PLT (DRISK) <input type="checkbox"/> OPDP (DDMAC) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DNRD review: 12/11/13, 11/20/13, 5/8/13
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM Filing Review: 5/31/13
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2) 12/23/13
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 1/7/14
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>October 2, 2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

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

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	1/7/14, 11/22/13, 9/25/13, 9/16/13, 9/3/13, 8/27/13, 7/10/13, 6/18/13, 6/3/13, 5/31/13 (74-day letter), 3/27/13 (acknowledgement letter)
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 11/5/12
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	n/a
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/16/14
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None 1/9/14
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	DNCE: 12/16/13 (final) DNP: 1/10/14
• Clinical review(s) <i>(indicate date for each review)</i>	DNCE: 12/16/13 (final) DNP: 1/10/14 DNCE: 5/17/13 (filing)
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested NAI letter: 10/21/13, CIS: 9/13/13
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/19/13 (final), 5/29/13 (filing)
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/19/13 (final), 5/29/13 (filing)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/20/13 (final), 5/29/13 (filing)
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/20/13 (final), 5/22/13 (filing)
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/17/13 (final), 5/17/13 (filing)
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/17/13 (final), 5/16/13 (filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None 11/8/13 (final), 4/23/13 (filing)
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 11/7/13 (final), 4/23/13 (filing)
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		FONSI: 5/2/13 Review: 5/2/13
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: 1/13/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

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

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

/s/

JADE A PHAM
01/22/2014

505(b)(2) ASSESSMENT

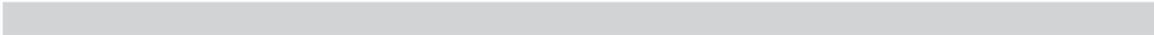
Application Information		
NDA # 205352	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Aleve PM Established/Proper Name: naproxen sodium and diphenhydramine hydrochloride Dosage Form: tablet Strengths: naproxen sodium 220 mg, diphenhydramine hydrochloride 25 mg		
Applicant: Bayer Healthcare		
Date of Receipt: 3/20/13		
PDUFA Goal Date: 1/20/14		Action Goal Date (if different): 1/17/14
RPM: Jade Pham		
Proposed Indication(s): For relief of occasional sleeplessness when associated with minor aches and pains; helps you fall asleep and stay asleep.		

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 by reliance on published literature, or by reliance on a final OTC monograph. *(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 listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Final monograph: Nighttime Sleep-Aid Drug Products For Over-The-Counter Human Use (21 CFR 338)	Safety and efficacy data including following specific sections to support proposed labeling: 21CFR338.10(a) – Active ingredient 21CFR338.50(c)(1) – Warning (do not use in children under 12 years) 21CFR338.50(c)(3) – Warning (glaucoma) 21CFR338.50(c)(4) – Warning (avoid alcoholic drinks) 21CFR338.50(c)(5) – Warning (do not use with other products containing DPH) 21CFR338.50(d)(1) – Directions (adults and children >12 years, 50 mg at bedtime)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 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 applicant is relying on the monograph for Nighttime Sleep-Aid Drug Products for Over-The-Counter Human Use (21 CFR 338) to support the safety and efficacy of diphenhydramine (DPH). Specifically, the applicant relies upon FDA’s Final Monograph for DPH to support the nonclinical safety of this component of the combination product. Additionally, the final monograph is relied upon to include labeling statements regarding the DPH component.

The proposed product contains diphenhydramine hydrochloride which is the active ingredient listed in the referenced final monograph. The DPH component is utilized as a night-time sleep aid. The proposed indication for the product is similar to indications listed in the final monograph for night-time sleep aids. The difference in indication related to the “minor aches and pains” claim is due to the naproxen component of the combination, which is supported by data from clinical studies conducted by the applicant.

The combination product is a tablet containing 25mg of DPH and the directions for use indicate that 2 caplets are to be taken at bedtime. This is also consistent with the final monograph which states that the oral dosage for DPH hydrochloride is 50 mg at bedtime.

Bayer conducted a BA study comparing the PK profiles of the active ingredients in the proposed combination product relative to currently marketed single ingredient products. Furthermore, Bayer provided sufficient quality/chemistry information to confirm that diphenhydramine HCl is an ingredient in the proposed product.

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 cited reliance on 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 #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

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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:

- 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 final OTC drug monograph? YES NO
If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug 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").

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 intended for the same route of administration 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), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

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?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

*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)?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
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

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):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (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

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/s/

JADE A PHAM
01/07/2014

From: Pham, Jade
To: ["Bill Walsh"](#)
Subject: NDA 205352 labeling IR
Date: Monday, January 06, 2014 4:38:00 PM

Hi Bill,

We need the following revisions to be made to the labeling for Aleve PM. Please respond no later than **COB, Wednesday, January 8th**.

- 1) Remove the symbol "+" from the PDP and spell out its intended meaning (i.e., "plus"). The plus symbol is an error prone symbol that has been mistaken for the number "4".
- 2) Revise the background color so the proposed Aleve PM can be easily distinguished from currently marketed Aleve and Aleve-D products. We request that you use a different background color to adequately

differentiate these products. The proposed [REDACTED] (b) (4) [REDACTED] and we are concerned that consumers will fail to recognize the differences between Aleve PM and Aleve or Aleve-D, and this confusion could lead to medication errors and result in adverse events.

Thanks,

Jade Pham, PharmD, MHSc
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Food and Drug Administration
Phone: 301-796-7031

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/s/

JADE A PHAM
01/06/2014

From: Pham, Jade
To: ["Bill Walsh"](#)
Cc: [Lee, Jung E \(OND\)](#)
Subject: NDA 205352 (Aleve PM)_labeling IR
Date: Friday, November 22, 2013 1:23:00 PM

Hi Bill,

We have the following comments pertaining to the labeling for NDA 205352 (Aleve PM)

- On the outer carton principal display panels and the immediate container front panels of all package sizes
 - Remove “(b) (4)” or replace it with a statement that makes it clear that the product is indicated to relieve difficulty sleeping as well as pain and does not use the phrase “(b) (4).”
 - 1 Break the statement, “sleep aid [plus] 12 hour pain relieving strength of Aleve” at a different point, such as between [plus] and 12, or show in some way that it is a single statement.
 - 2 Add an asterisk next to “Caplets” and an asterisk before the definition of the dosage form, “capsule-shaped tablets.”
- On the outer carton and 2-count pouch Drug Facts and the immediate container back panels of all package sizes
 - Remove “(b) (4)” from **Questions or comments?** or submit (b) (4) for review as labeling.
- On the 20-, 40-, and 80-count outer cartons
 - A banner stating, “New” appears on the upper right corner of the Principal Display Panel. Language should be added to explain that the product itself is new. The banner may remain in place for 6 months of marketing.
 - 1 Add an instruction to the outer carton to read and keep the outer carton. This could stand alone or be added under **Other information**.
- On the 20-, 40-, and 80-count immediate container labels
 - Add “Drink a full glass of water with each dose” to **Directions** on the immediate containers or change (b) (4)
- On the 20- and 40-count immediate container labels and the 2-count pouch
 - Add a period at the end of the symptoms of allergic reaction, as follows, “...• rash • blisters[insert period] If an allergic reaction...” to separate the list from the following sentence.
- On the 80-count immediate container label
 - Consider using a peel-back Drug Facts label so that additional information, including the complete allergy alert, will be readily available at the point of use.
- On the 20-count outer carton,
 - Increase the spaces between bullets and preceding text to at least two square ems as required in 201.66(d)(4).
 - 1 Remove the parentheses from the signs and symptoms of stomach bleeding under *Stop use and ask a doctor if* to conform with 201.326(a)(2)(iii)(C).

- On the 2-count pouch
- Show the locations of the lot number and expiration date as required in 21 CFR 201.17, 211.132, and 201.18.

Please respond no later than Friday, December 6, 2013. Also, please note that I will be out of the office from November 28 (Thanksgiving) through December 6. Please be sure to send a courtesy email to me and Jung Lee (cc'd above) on your response since Jung will be covering for me during the time that I am away.

Thanks,

Jade Pham, PharmD, MHSc
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Food and Drug Administration
Phone: 301-796-7031

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/s/

JADE A PHAM
11/22/2013

PeRC PREA Subcommittee Meeting Minutes
October 2, 2013

PeRC Members Attending:

Lynne Yao
Hari Cheryl Sachs
Karen Davis-Bruno
Tom Smith
Andrew Mulberg (Did not review Kaletra, Intelence, Aleve PM)
Wiley Chambers
Donna Katz
Robert “Skip” Nelson
Shrikant Pagay
Lily Mulugeta
Andrew Mosholder
Kevin Krudys
Barbara Buch
Susan McCune
Daiva Shetty
Martha Nguyen
Peter Starke
Ruthianna Davi
Gregory Reaman
Jane Inglese
William Rodriguez
George Greeley
Coleen LoCicero
Robert “Skip” Nelson
Rachel Witten
Maura O’Leary

Guests Attending:

Nichella Simms (PMHS)	Amy Taylor (PMHS)
Erica Radden (PMHS)	GT Wharton (OPT)
Courtney Suggs (OCP)	Gilbert Burckart (OCP)
Donna Snyder (PMHS)	Robert Levin (DPP)
Dionna Green (OCP)	Owen McMaster (DAIP)
Alison Rodgers (DAIP)	Ronald L. Ariagno (OPT/PMHS)
Jian Wang (OCP)	Ellen Fields (DAAAP)
Elizabeth Kilgore (DAAAP)	Dominic Chiapperino (DAAAP)
Aisar Atrakdei (DPP)	Kim Updegraff (DPP)
Hao Zhu (OCP)	Yun Xu (OCP)

Agenda

(b) (4)



(b) (4)



(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Aleve PM Partial Waiver/Assessment

- NDA 205352, Aleve PM (naproxen sodium) tablet, seeks marketing approval for relief of occasional sleeplessness when associated with minor aches and pains and helps you fall asleep and stay asleep.
- The supplement was received on March 20, 2013 and has a PDUFA goal date of January 20, 2014.
- The application triggers PREA as a new active ingredient.

(b) (4)

PeRC Recommendations

- The PeRC recommend to the Division that a partial waiver be granted in patients ages birth to less than 12 years because the product would be ineffective and/or unsafe. This is consistent with labeling for other OTC products for this indication.
- For those patients 13 to 17 years, the PeRC noted that a pediatric assessment could be provided because the sponsor provided data in the application for patients down to 12 years of age. Therefore, a waiver in patients 12 to less than 17 years of age is not necessary.

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/s/

GEORGE E GREELEY
11/06/2013

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/s/

ANTOINE N EL HAGE
10/21/2013

SUSAN D THOMPSON
10/21/2013

Rivera, Luz E (CDER)

From: Leonard Baum <leonard.baum@bayer.com>
Sent: Thursday, September 12, 2013 8:28 AM
To: McKnight, Rebecca; Rivera, Luz E (CDER)
Subject: RE: IR Questions for NDA 205352

Good morning,

We are currently working on the formal request and should be able to send our response towards end of next week. We will send a copy via e mail and then follow up with the official submission to our eCTD

[please let me know if you have any questions.

Regards

Len

Len Baum, RPh
Vice President
Regulatory Affairs
Bayer Healthcare
Consumer Care
Ph:862-404-4672

From: McKnight, Rebecca [mailto:Rebecca.McKnight@fda.hhs.gov]
Sent: Wednesday, September 11, 2013 12:19 AM
To: Leonard Baum
Cc: Rivera, Luz E (CDER)
Subject: RE: IR Questions for NDA 205352

Hi Len,

Please respond to Luz Rivera. I will be on leave until 09/30.

Thanks,
Becky

From: Leonard Baum [mailto:leonard.baum@bayer.com]
Sent: Monday, September 09, 2013 2:44 PM
To: McKnight, Rebecca
Subject: RE: IR Questions for NDA 205352

Hi Becky,

I am checking with our CMC group and will let you know how long it may be for submission.

Len

Len Baum, RPh
Vice President
Regulatory Affairs
Bayer Healthcare

Consumer Care
Ph:862-404-4672

From: McKnight, Rebecca [<mailto:Rebecca.McKnight@fda.hhs.gov>]
Sent: Monday, September 09, 2013 11:51 AM
To: Leonard Baum
Subject: RE: IR Questions for NDA 205352

Hi Len,

If you can send an email copy to me and submit an amendment to the NDA, that would be great. Also, do you have a timeframe that I can give to the reviewer on when to expect a response?

Thanks,
Becky

From: Leonard Baum [<mailto:leonard.baum@bayer.com>]
Sent: Monday, September 09, 2013 11:43 AM
To: McKnight, Rebecca
Subject: RE: IR Questions for NDA 205352

Thanks for sending, and tracking me down. We will prepare a response and submit to NDA with copy to you... or is there another way you want us to respond?

Regards
Len

Len Baum, RPh
Vice President
Regulatory Affairs
Bayer Healthcare
Consumer Care
Ph:862-404-4672

From: McKnight, Rebecca [<mailto:Rebecca.McKnight@fda.hhs.gov>]
Sent: Monday, September 09, 2013 9:25 AM
To: Leonard Baum
Subject: IR Questions for NDA 205352

Dear Mr. Baum,

We are reviewing NDA 205352, and have the following questions pertaining to the CMC portion of your application:

1. As per 314.54(a)(1)(i), 505(b)(2) applications must provide a master batch record or a proposed master batch record. We note that you have provided executed batch records. Submit a master batch record, proposed master batch record, or confirm that the executed batch records in Module 3.2.R is identical to the master batch record for the intended commercial manufacturing process.
2. The application must contain a commercial scale master batch record or a comparably detailed manufacturing process description. This information is submitted under Module 3.2.P.3.3 "Description of Manufacturing Process and Process Controls". Your manufacturing process description is not comparably detailed to a master

- batch record. The manufacturing process description (or master batch record) must contain process parameter ranges and targets for all unit operations and a description of the equipment type and scale.
3. There is only one set of regulatory specifications in an NDA submission. Your drug product must meet this set of specifications throughout the claimed product shelf life. However, it is permissible that you maintain an internal set of release specifications. In your application, this internal set of release specifications can be discussed as part of your overall control strategy. Resubmit the drug product specifications to align with the end of shelf-life specifications and classify the release specifications an internal set of specifications part of your overall control strategy.
 4. For drug substance unidentified impurities, report all individual impurities \geq (b) (4) % of the diphenhydramine HCl label claim identified by the relative retention time to be consistent with the ICH Q3B reporting limit.
 5. Confirm for Tables 10 and 11 in “pharm-development-manufac-process” that the final boxes for “AV-value of Napso (Target \leq (b) (4))” should actually read “AV-value diphenhydramine HCl (Target \leq (b) (4))”.

Please provide your response via email to me and as an amendment to your application.

Thank you,

Rebecca McKnight
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
CDER-ONDQA-FDA
301-796-1765

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/s/

LUZ E RIVERA
09/25/2013

From: [Peacock, Celia](#)
To: bill.walsh@bayer.com
Cc: [Peacock, Celia](#); [Pham, Jade](#)
Subject: NDA 205352 September 5 Information Request
Date: Thursday, September 05, 2013 11:23:11 AM

Hi Bill. We have an additional information request:

1. Please provide the verbatim terms for the dataset ADAE for Study 14837 by September 13th.

Thank you.

Celia

Celia R. Peacock, MPH, RD
Senior Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
WO22 - Room 5416
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.4154
Fax 301.796.9897
celia.peacock@fda.hhs.gov

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/s/

JADE A PHAM
09/16/2013

From: [Peacock, Celia](#)
To: bill.walsh@bayer.com
Cc: [Peacock, Celia](#); [Pham, Jade](#)
Subject: NDA 205352 September 3 Information Request
Date: Tuesday, September 03, 2013 3:08:58 PM

Good Afternoon Bill. We have the following request for information.

1. We note that over-encapsulated tablets were used in your pivotal clinical studies. However, we are unable to locate any data bridging the capsule formulation with the proposed commercial tablet. Provide the comparative dissolution profile data (individual

values, mean, RSD, f2 statistic) using the proposed dissolution method for the over-encapsulated clinical trial material compared with the un-encapsulated referenced tablets (lot 59541P0) (n =12) demonstrating similar dissolution performance between the

products. Please note that significant differences in dissolution may need to be further supported with bioequivalence data.

(2) Your proposed acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes is not acceptable. Absent clinical data to justify wider tolerances, the dissolution acceptance criterion should reflect the earliest time point where $> \frac{(b)}{(4)}\%$ dissolution is occurring. Your data support a final acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes for both APIs. Implement this change and provide a revised drug product specification table incorporating the updated dissolution acceptance criterion

Thank you.

Celia Peacock
(For Jade Pham)

Celia R. Peacock, MPH, RD

Senior Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
WO22 - Room 5416
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.4154
Fax 301.796.9897
celia.peacock@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

CELIA R PEACOCK
09/03/2013

From: [Bill Walsh](#)
To: [Pham, Jade](#)
Cc: [Fitch, Johann M](#); [Leonard Baum](#)
Subject: NDA 205352 (Aleve PM) Check In
Date: Thursday, August 22, 2013 3:40:02 PM
Attachments: [emfalert.txt](#)

Hi Jade-

Just wanted to drop a line to let you know that I will be on vacation from August 26th returning September 3rd. In the event you have any questions or data requests, please contact Len Baum at leonard.baum@bayer.com or at (b) (6).

One additional note:

During the pre-approval FDA audit at PPD Development, LLP (William Buchanan, MD, DDS – Principal Investigator) for Study # 14837, it was noted on data listing 16.2.5 that the variable TSSDA was incorrectly defined as “time between *end* of surgery and study drug administration.” The TSSDA should have been defined as “time between *beginning* of surgery and study drug administration.” Because the TSSDA was only displayed in the data listing and not used for any other statistical analyses, there is no impact on the study results and Bayer has no plans to submit a correction to the TSSDA calculation error. Per his request, I have copied the FDA Site Inspector (b) (4) on this e-mail.

Freundliche Grüße / Best regards,
Bill Walsh
Director
US Regulatory Affairs & Regulatory Operations



Science For A Better Life
Bayer HealthCare LLC
BHC-CC-R&D-REGU-REGU
Morristown,
Tel: +1 973 408 8046
Fax:
E-mail: bill.walsh@bayer.com
Web: <http://www.bayerhealthcare.com>

Vorstand: Jörg Reinhardt, Vorsitzender | Hartmut Klusik, Manfred Vehreschild
Vorsitzender des Aufsichtsrats: Richard Pott
Sitz der Gesellschaft: Leverkusen | Eintragung: Amtsgericht Köln, HRB 62445

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/s/

JADE A PHAM
08/27/2013

From: Pham, Jade
To: ["Bill Walsh"](#)
Subject: NDA 205352 (Aleve PM): information request
Date: Thursday, August 01, 2013 2:54:00 PM

Hi Bill,

We have an additional information request:

For PK study 16135, the AE dataset does not include the treatment arm. Please re-send the data set including the treatment for each patient and when the event occurred.

Please send the updated AE dataset by August 7th.

Thanks,
Jade

Jade Pham, PharmD, MHSc
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Food and Drug Administration
Phone: 301-796-7031

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/s/

JADE A PHAM
08/01/2013

From: Pham, Jade
To: ["Bill Walsh"](#)
Subject: NDA 205352 (Aleve PM): information request
Date: Wednesday, July 10, 2013 1:29:00 PM

Hi Bill,

We have the following information request pertaining to NDA 205352:

The adverse event dataset (ADAE.xpt) from the multiple dose safety study (15560) has errors that prevents us from conducting analyses. For example, it contains unusual character trails (^M) in the terms in the AETERM, AEPT columns. Please check all columns for such character trails and resend the data set within one week after deleting these character trails. In addition, the Data Analysis Define File has been provided in DEFINE.XML format. Please provide the Define file in PDF format within one week.

Thanks,
Jade

Jade Pham, PharmD, MHSc
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Food and Drug Administration
Phone: 301-796-7031

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/s/

JADE A PHAM
07/10/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205352

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bayer Healthcare – Consumer Care
36 Columbia Rd
P.O. Box 1910
Morristown, NJ 07962-1910

Attention: William R. Walsh, RPh.
Director
U.S. Regulatory Affairs & Regulatory Operations

Dear Mr. Walsh:

Please refer to your New Drug Application (NDA) dated and received March 20, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Naproxen Sodium and Diphenhydramine HCL Tablets, 220 mg/25 mg.

We also refer to your correspondence dated and received March 28, 2013, requesting review of your proposed proprietary name, Aleve PM. We have completed our review of the proposed proprietary name, Aleve PM, and have concluded that it is acceptable.

The proposed proprietary name, Aleve PM, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If **any** of the proposed product characteristics as stated in your March 28, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Jeffrey Buchanan at (301)796-1007.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
06/24/2013

From: Pham, Jade
To: "[Bill Walsh](#)"
Subject: RE: NDA 205352 Aleve PM - 74-day letter
Date: Friday, June 14, 2013 2:32:00 PM

Hi Bill,

Please see below highlighted in red, responses to your requests for clarification.

If you have any additional questions, please feel free to email me.

Thanks,
Jade

From: Bill Walsh [mailto:bill.walsh@bayer.com]
Sent: Friday, June 07, 2013 12:26 PM
To: Pham, Jade
Subject: RE: NDA 205352 Aleve PM - 74-day letter

Hi Jade-

As promised, here are some requests for clarification we have related to FDA's review issues identified in the 74- Day Letter. (I have included FDA's issue from the letter for ease of review.)

FDA Issue #3.

Your dissolution method development and validation information is incomplete. Please provide the following:

The complete dissolution method development report, which includes your database justification for the selected dissolution apparatus and agitation speed as optimal for your product, and provide the pH solubility profile of each drug substance. We were able to locate only your justification for the proposed dissolution medium in the NDA.

The results of the studies completed to evaluate the discriminating ability (i.e., the method's ability to detect meaningful manufacturing variations) of your proposed dissolution method for review.

Bayer Response to #3:

We have included dissolution method development information in document P.2.2.02 (pharm-development-dissolution-profiles). Included in this report, we provided justification of the pH 7.4 dissolution medium and conditions that are based on the USP "Naproxen Sodium Tablets" monograph. As requested, we will provide data on the agitation speed, apparatus, and the solubility of the drug substances.

Additionally, we will provide supportive data that includes the variation of the following parameters:

1. API quantity (by variation of tablet weight)
2.  (b) (4)
3.  (b) (4)
4.  (b) (4)

(b) (4)

(b) (4) weight

Naproxen sodium, which has a (b) (4), is present at over (b) (4) of the tablet weight and therefore significantly influences the (b) (4). The mechanism of tablet release (b) (4).

(b) (4) The results will be summarized and presented in our official response .

Does the plan provide adequate information to make your evaluation?

Yes

FDA Issue #4. Your batch analyses and stability data include only single-point dissolution at (b) (4) minutes, which is inadequate for review. Provide the complete dissolution profile data for each pivotal clinical and registration batch (10, 15, 20, 30, 45, and 60 minutes) at release. If release data are not available, we request that you collect the dissolution data using appropriate remaining samples. The source and storage conditions for the samples used should be specified. Also, add complete dissolution profile sampling to your next and future stability pulls and provide an update in a future amendment to your NDA.

Bayer Response to #4:

Dissolution profile data of the three registration batches (6662, 6663, and 6664) and the clinical batch (59541P0) are included in document P.2.2.02 (pharm-development-dissolution-profiles). These samples were taken from the 12 month stability pull (stored at 25°C/60% RH in the 38 cc HDPE bottle). Profiles were generated at the specified timepoints (10, 15, 20, 30, 45, and 60 minutes) at the three physiological pHs (1.2, 4.5, 6.8) and at the selected pH of 7.4.

Since these profiles have already been included in the submission, do you still request that we conduct profiling at the next and future stability pulls for the registration batches?

Yes. Please continue to collect the dissolution profile data on the remaining pulls for the registration batch.

FDA Issue #6. For the Bayer pharmacovigilance database, provide a tabular case-by-case summary for the serious case reports and deaths with the following column headings: Case ID Age, Gender, DPH dose, Route of Administration, Suspect Medications, Concomitant Medications, Reported Adverse Events in MedDRA Preferred Terms, Outcome, Narrative Summary, and Comments. Provide a discussion and analysis of these reports.

Bayer Response to #6:

Bayer will provide tables with the requested columns, minus the column for the narratives which may be read from the CIOMS reports which will be attached to the report as an appendix. Two tables will be provided; one for fatal reports, the other for non-fatal serious reports. A brief analysis and discussion will follow each table, providing an aggregate view of these data.

Is this proposal acceptable to FDA?

Yes, this is acceptable. We would also like you to provide the data in electronic form with hyperlinks to the individual CIOMS reports. In this dataset:

- add a column noting the indication diphenhydramine was used for and another column indicating the source of the report, e.g., medical professional, AAPCC, consumer, or literature
- provide a unique identifier for each subject so we can cross reference the CIOMS forms with MedWatch forms that may have been submitted to FDA. The manufacturer control number may serve this purpose.

Please let me know if you have any questions.

Freundliche Grüße / Best regards,
Bill Walsh
Director
US Regulatory Affairs & Regulatory Operations



Science For A Better Life
Bayer HealthCare LLC
BHC-CC-R&D-REGU-REGU
Morristown,
Tel: +1 973 408 8046
Fax:
E-mail: bill.walsh@bayer.com
Web: <http://www.bayerhealthcare.com>

Vorstand: Jörg Reinhardt, Vorsitzender | Hartmut Klusik, Manfred Vehreschild
Vorsitzender des Aufsichtsrats: Richard Pott
Sitz der Gesellschaft: Leverkusen | Eintragung: Amtsgericht Köln, HRB 62445

From: Bill Walsh [<mailto:bill.walsh@bayer.com>]
Sent: Friday, May 31, 2013 3:07 PM
To: Buchanan, Jeffrey A.
Cc: Pham, Jade
Subject: RE: NDA 205352 Aleve PM - 74-day letter

Thanks Jeff. We'll get right on these items. Appreciated your help on this project and sorry to lose you.

Jade, looking forward to working with you and I will get back to you with any questions.

Have a good weekend.

Freundliche Grüße / Best regards,
Bill Walsh
Director
US Regulatory Affairs & Regulatory Operations



Science For A Better Life

Bayer HealthCare LLC
BHC-CC-R&D-REGU-REGU
Morristown,
Tel: +1 973 408 8046
Fax:
E-mail: bill.walsh@bayer.com
Web: <http://www.bayerhealthcare.com>

Vorstand: Jörg Reinhardt, Vorsitzender | Hartmut Klusik, Manfred Vehreschild
Vorsitzender des Aufsichtsrats: Richard Pott
Sitz der Gesellschaft: Leverkusen | Eintragung: Amtsgericht Köln, HRB 62445

From: Buchanan, Jeffrey A. [<mailto:Jeffrey.Buchanan@fda.hhs.gov>]
Sent: Friday, May 31, 2013 2:58 PM
To: Bill Walsh
Cc: Pham, Jade
Subject: NDA 205352 Aleve PM - 74-day letter
Importance: High

Hi Bill,

Attached is your 74-day letter for Aleve PM. There were no filing issues, but there are 7 review issues you'll need to address within 45 days (by July 15, 2013). If you cannot meet the 45-day deadline, please let us know as soon as possible.

In closing, I will no longer be the assigned Project Manager for this application. From this point forward, you should contact Dr. Jade Pham, DNCE RPM, at 301-796-7031 or jade.pham@fda.hhs.gov. Thanks.

Jeff Buchanan

Regulatory Health Project Manager
Division of Nonprescription Clinical Evaluation (DNCE)
FDA/CDER/OND, Office of Drug Evaluation IV
10903 New Hampshire Ave., WO22 Room 5473
Silver Spring, MD 20903
Phone: 301-796-1007 Fax: 301-796-9899
jeffrey.buchanan@fda.hhs.gov

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/s/

JADE A PHAM
06/03/2013



NDA 205352

FILING COMMUNICATION

Bayer Healthcare, LLC – Consumer Care
Attention: Leonard Baum, R.Ph.
Vice President, Regulatory Affairs, North America
36 Columbia Road
Morristown, NJ 07962

Dear Mr. Baum:

Please refer to your New Drug Application (NDA) dated March 20, 2013, received March 20, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Aleve PM (naproxen sodium, 220 mg, and diphenhydramine hydrochloride, 25 mg) tablets.

We also refer to your amendments dated March 28, April 18, and May 15, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 20, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 23, 2013.

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

During our filing review of your application, we identified the following review issues. We request that you submit the following information by July 15, 2013:

1. The Define documents for both Study 14837 and 15881 are not adequate. Please provide updated Define documents in PDF format. The Define documents should include sufficient description for each variable in the comments field. If a variable is discrete, each value or category should be clearly defined. For example, for dataset ADACT in Study 14837, there is no description for the values or categories for SLSCAT, SLSPID, SAF and ITT. For derived variables, the method for calculating the variable should be included in the comments field. For raw variables in clinical datasets, the location of the variable on the annotated CRF should be provided as well as the CRF field name if different from the variable name in the dataset. For more details regarding requirements for Define documents, please refer to Study Data Specifications Version 2.0 (July 18, 2012).
2. Relative to product labeling, please submit the following:
 - an outer carton label for the 2-count pouch SKU or, if there is no outer carton, a description of how the pouches will be displayed and sold
 - a list of all SKUs to be sold under this NDA and labels for any SKUs that were not submitted.
3. Your dissolution method development and validation information is incomplete. Please provide the following:
 - The complete dissolution method development report, which includes your data-based justification for the selected dissolution apparatus and agitation speed as optimal for your product, and provide the pH solubility profile of each drug substance. We were able to locate only your justification for the proposed dissolution medium in the NDA.
 - The results of the studies completed to evaluate the discriminating ability (i.e., the method's ability to detect meaningful manufacturing variations) of your proposed dissolution method for review.
4. Your batch analyses and stability data include only single-point dissolution at (b) (4) minutes, which is inadequate for review. Provide the complete dissolution profile data for each pivotal clinical and registration batch (10, 15, 20, 30, 45, and 60 minutes) at release. If release data are not available, we request that you collect the dissolution data using appropriate remaining samples. The source and storage conditions for the samples used should be specified. Also, add complete dissolution profile sampling to your next and future stability pulls and provide an update in a future amendment to your NDA.
5. Provide narrative summaries for subjects who:
 - dropped out or withdrew from PK study 16135
 - did not complete study 14837.
6. For the Bayer pharmacovigilance database, provide a tabular case-by-case summary for the serious case reports and deaths with the following column headings: Case ID Age, Gender, DPH dose, Route of Administration, Suspect Medications, Concomitant

Medications, Reported Adverse Events in MedDRA Preferred Terms, Outcome, Narrative Summary, and Comments. Provide a discussion and analysis of these reports.

7. In the nonclinical section of Module 2 of your NDA, it would assist our review if you provided a summary of the nonclinical information for each of the active ingredients, and address whether there are any potential interactions between the two active ingredients. Please also provide a justification as to why you consider the levels of inactive ingredients, impurities, and degradants present in your proposed drug product as safe for human use.

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

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

(b) (4)

If you have questions, contact Jeff Buchanan, Regulatory Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Shaw Chen, M.D., Ph.D.
Acting Division Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

SHAW T CHEN
05/31/2013



NDA 205352

NDA ACKNOWLEDGMENT

Bayer Healthcare, LLC – Consumer Care
Attention: Leonard Baum, R.Ph.
Vice President, Regulatory Affairs, North America
36 Columbia Road
Morristown, NJ 07962

Dear Mr. Baum:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Aleve PM (naproxen sodium, 220 mg, and diphenhydramine hydrochloride, 25 mg) tablets

Date of Application: March 20, 2013

Date of Receipt: March 20, 2013

Our Reference Number: NDA 205352

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 19, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have questions, contact me at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Jeffrey Buchanan
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

JEFFREY A BUCHANAN
03/27/2013

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

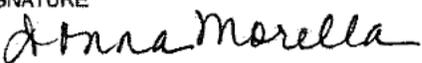
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the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

Please mark the applicable checkbox.

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

Clinical Investigators	See attached	

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

NAME Donna Morella	TITLE Senior Manager, Global Clinical Operations
FIRM/ORGANIZATION Bayer HealthCare Consumer Care	
SIGNATURE 	DATE (mm/dd/yyyy) 12/18/12

Paperwork Reduction Act Statement

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

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

1.3.4 Financial Disclosure Form

List of Investigators (*Subinvestigators*) for Clinical Studies Submitted in Support of This Application

Bayer Study 13053 - Pilot Study

Steven E. Christensen, DDS

(b) (4)

Jean Brown Research
1045 E. 3900 South, Suite 100
Salt Lake City, UT 84124

Bayer Study 14837 – Dose Selection Efficacy Study

William L. Buchanan, MD, DDS

(b) (4)

PPD Development, LP
7551 Metro Center Drive, Suite 200
Austin, TX 78744

Patrick R. Brain, DDS

(b) (4)

Jean Brown Research
1045 E. 3900 South, Suite 100
Salt Lake City, UT 84124

Bayer Study 15881 – Efficacy, Lower DPH

William L. Buchanan, MD, DDS

(b) (4)

PPD Development, LP
7551 Metro Center Drive, Suite 200
Austin, TX 78744

Lynn R. Webster, MD

(b) (4)

Lifetree Clinical Research
3838 South 700 East, Suite 200
Salt Lake City, UT 84106

Bayer Study 15560 - Maximum Use Safety Study

Steven H. Barag, DO
(b) (4)

Rancho Cucamonga Clinical Trials
7974 Haven Avenue, Suite 268
Rancho Cucamonga, CA 91730

Christopher M. Chappel, MD
(b) (4)

FPA Clinical Research
222 Broadway Avenue, Suite 302
Kissimmee, FL 34741

Donna M. DeSantis, MD
(b) (4)

East Valley Physicians/Clinical
Research Advantage
1455 W. Chandler Blvd.
Bldg A, Suite 1
Chandler, AZ 85224

Richard S. Dobrusin, DO
(b) (4)

Mesa Family Medical Center/ Clinical
Research Advantage
1345 E. McKellips Road, Suite 106
Mesa, AZ 85203

David L. Fried, MD

(b) (4)

Omega Medical Research
400 Bald Hill Road
Warwick, RI 02886

Walter Y. Chi, MD

(b) (4)

Centennial Medical Group
8186 Lark Brown Road
Elkridge, MD 21075

Robert Joseph Jeanfreau, MD

(b) (4)

Benchmark Research
3800 Houma Blvd., Suite 345
Metairie, LA 70006

Timothy L. Grant, MD

(b) (4)

Miami Research Associates
6141 Sunset Drive, Suite 301
Miami, FL 33143

Richard Braden Neiman, MD

(b) (4)

Integra Clinical Research
3603 Paesanos Pkwy, Suite 120
San Antonio, TX 78231

Ivan H. Rarick II, MD

(b) (4)

Benchmark Research
3701 J Street, Suite 220
Sacramento, CA 95816

Nathan Segall, MD, CPI

(b) (4)

Clinical Research Atlanta
175 Country Club Drive, Suite 100A
Stockbridge, GA 30281

William M. Seger, MD

(b) (4)

Benchmark Research
4504 Boat Club Road, Suite 400A
Ft. Worth, TX 76135

John F. Speer, MD

(b) (4)

Colorado Springs Health Partners – East
Clinical Research Advantage
6340 Barnes Road
Colorado Springs, CO 80922

Cynthia Becher Strout, MD

(b) (4)

Coastal Carolina Research
1156 Bowman Road, Suite 102
Mt. Pleasant, SC 29464

Kyle Patrick, DO

(b) (4)

Premier Research Group
13128 N. 94th Drive, Suite 200
Peoria, AZ 85381

Lynn Roy Webster, MD

(b) (4)

LifeTree Clinical Research
3838 S. 700 East, Suite 202
Salt Lake City, UT 84106

Peter John Winkle, MD

(b) (4)

Advanced Clinical Research Institute
1211 West La Palma, Suite 303
Anaheim, CA 92801

Steven Zeig, MD

(b) (4)

Pines Clinical Research
601 N. Flamingo Road, #104
Pembroke Pines, FL 33028



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103407

MEETING MINUTES

Bayer Health Care Consumer Care
Attention: Priti C. Lad, Pharm. D.
Manager, Regulatory Affairs
P.O. Box 1910
Morristown, NJ 07962-1910

Dear Ms. Lad:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aleve[®] PM (naproxen sodium and diphenhydramine).

We also refer to the teleconference between representatives of your firm and the FDA on October 9, 2012. The purpose of the meeting was to obtain FDA feedback regarding your proposed content and format of your planned NDA.

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

If you have any questions, call Daniel Reed, Regulatory Project Manager at (301) 796-2220.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: IND

Meeting Date and Time: October 9, 2012
Meeting Location: Teleconference

Application Number: 103407
Product Name: Aleve[®] PM (naproxen sodium and diphenhydramine)
Indication: Relief of occasional sleeplessness due to pain
Sponsor/Applicant Name: Bayer Health Care Consumer Care

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

Meeting Recorder: Melissa Furness
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation

Andrea Leonard-Segal, M.D. M.S., Director
Joel Schiffenbauer, M.D., Deputy Director
Lesley Furlong, M.D., M.S., Medical Team Leader
Christina Chang, M.D., M.P.H., Medical Officer
Cindy Li, Ph.D., Pharmacologist/Toxicologist
Melissa Furness, Chief, Project Management Staff
Dan Reed, Regulatory Health Project Manager

Division of Nonprescription Regulation Development
Kathleen Phelan, R.Ph., Interdisciplinary Scientist

Division of Neurology Products

Veneeta Tandon, Ph.D, Clinical Reviewer
Ronald Farkas, M.D., Ph.D., Medical Team Leader

Division of Anesthesia, Analgesia and Addictive Drug Products

Christina Fang, M.D., Medical Officer

Office of Biometrics

Sharon Yan, Ph.D., Statistical Reviewer
Yan Zhou Ph.D., Statistical Reviewer

Office of Clinical Pharmacology
Yang Xinning Ph.D., Clinical Pharmacology Reviewer

Division of New Drug Quality Assessment III
Xavier Ysern, Ph. D., CMC Reviewer

SPONSOR ATTENDEES

Bayer Consumer Healthcare

Irene Laurora, PharmD, Vice President, Medical Affairs
Sistine Jarvis, Director, Medical Affairs
Leonard Baum, RPh, Vice President, Regulatory Affairs
Bill Walsh, RPh, Director, Regulatory Affairs
Priti C. Lad, PharmD Manager, Regulatory Affairs
Robert An, PhD, Senior Associate Director, Biostatistics

Bayer's Consultants

(b) (4)

1.0 BACKGROUND

Bayer Consumer Healthcare (Bayer) submitted a meeting request to the FDA on April 20, 2012 to obtain the Agency's feedback regarding their proposed content and format of the planned NDA for Aleve PM (naproxen sodium and diphenhydramine). A type B meeting was granted and scheduled for October 9, 2012. On October 4, 2012 FDA sent preliminary response to Bayer in response to the questions submitted in their August 27, 2012 meeting background package. The questions from Bayer appear in section 2.0 below, each followed by the preliminary FDA responses in italicized text. Questions 1, 5, & 9 were discussed at the October 9, 2012 meeting. A record of the discussion that occurred during the meeting is presented following questions 1, 5, & 9.

Additionally, Bayer requested feedback on their proposed tag line on their planned Principal Display Panel (PDP) that was sent to the Agency via an e-mail correspondence on October 5, 2012 (please refer to section 5 of this document). The Agency agreed to provide feedback to Bayer's proposal as a post-meeting addendum (please refer to section 6 of this document).

2.0 QUESTIONS

1. Does the Agency have any questions or comments regarding the clinical program or data presentation as outlined in the pre-meeting background package or need additional information in the NDA in order to help facilitate its review? (Section 4, Clinical Development Program)

FDA Preliminary response:

The efficacy of your proposed dose appears to be supported by one trial (study # 14837). You should provide a rationale for why the data from this study alone would be considered adequate to demonstrate evidence of efficacy for this product.

Please include efficacy analyses for Studies 14837 and 15881 by subgroups of age, gender, baseline pain severity and other relevant characteristics. Please provide a comprehensive presentation of data for rescued patients, including the number (%) of patients rescued by hour and in total, before and after sleep onset, and by baseline pain severity.

Discussion:

Bayer stated their assessment that the totality of their drug product development program was adequately supportive of their planned NDA. In the application, Bayer intends to use data from this program to demonstrate why naproxen sodium 440 mg/diphenhydramine 50 mg was selected as the final dose, and why naproxen sodium 440 mg/diphenhydramine 25 mg was not selected. The Agency reiterated that, in their NDA, Bayer will need to provide their scientific rationale for why they believe their one study (study # 14837) and the totality of their drug development program adequately support their application.

Bayer inquired if the requested subgroup analyses could be included in their Integrated Summary of Efficacy (ISE). The Agency requested that the subgroup analyses be included in the individual study reports under Clinical Study Report in Module 5. Bayer asked if they could include the requested subgroup analyses as addendums to each study report as some of the reports were already finalized. The Agency agreed that this was acceptable.

2. Does the Agency have any questions or require any additional information in the NDA regarding the dose selection rationale in order to facilitate its review? (Section 5, Dose-Selection)

FDA Preliminary response:

Please refer to our response to Question 1 above.

3. In this pre-NDA background package, Bayer has summarized the demographic characteristics of the population that was enrolled in the Multiple Dose Safety Study. Does the Agency agree that the study population adequately represents the target population for this OTC combination product? (Section 4.3.4, Multiple-Dose Safety Study)

FDA Preliminary Response:

The information summarized in the briefing material suggests the study population reasonably reflects the intended target population of this combination product. Our final determination will be made following a thorough review of study results.

4. Bayer conducted two pivotal efficacy studies with the investigational product and one proof of concept pilot study with currently marketed products. Bayer will present the information from these studies in the integrated summary of efficacy and safety (see Table 4.1.3 in this document for an example). Due to differences in the study methodology between these studies, these data will not be pooled. Does the Agency agree with this approach? (Section 4, Clinical Development Program)

FDA Preliminary Response:

We agree that the studies need not be pooled.

5. Per Agency request for information regarding the potential for next day effects of diphenhydramine, Bayer has prepared a summary of diphenhydramine safety data, which includes a diphenhydramine literature review and the safety data gathered from the clinical studies, including the diphenhydramine plasma concentrations from the PK study. Does the Agency have any questions regarding this information to be provided in the NDA submission in order to facilitate its review? (Section 6.1, Diphenhydramine (DPH) Safety Data)

FDA Preliminary Response:

We note that there are additional publications pertaining to next day effects of diphenhydramine that are not included in your literature review (for example, Katayose 2012). We recommend that you provide a comprehensive, up-to-date literature review with respect to diphenhydramine and next-day effects. Please include in the NDA submission complete literature references with full articles.

We also recommend that the analysis of the DPH postmarketing information give particular focus to events suggesting next-day functional impairment, such as motor vehicle accidents, falls, or hypersomnolence. The use of the "Accidents and injuries" standardized MedDRA query (SMQ) may be helpful.

Discussion:

The Agency requested that Bayer submit a comprehensive literature review (relevant to the proposed use for this drug product). Bayer indicated that they have already conducted a literature search through May 2012. Bayer proposed to submit relevant articles published after May 2012 in the four-month safety update in the NDA. The Agency stated that this approach was acceptable.

In addition to presenting a standard postmarketing safety review for both active ingredients in the NDA, the Agency requested that Bayer also provide a targeted analysis of postmarketing safety information for diphenhydramine, focusing on adverse events pertinent to next-day residual effects as related to the nighttime administration of diphenhydramine for sleep. Bayer agreed to provide the requested information.

6. Does the FDA have any questions with Bayer's plan for submitting post marketing safety reports in the NDA for the intervals as outlined in this pre-meeting background package? (Section 6.2, Post-Marketing Safety Data)

FDA Preliminary Response:

Your proposed plan appears reasonable.

7. Does the FDA agree with the proposed data lock point for the 4-month safety update report as outlined in Section 6.2, Postmarketing Safety Data, of this submission?

FDA Preliminary Response:

Your proposal to use the NDA submission date as the data lock point for the 4-month safety update report is acceptable.

8. Proposed Drug Facts labeling is provided in this pre-meeting background package. The proposed labeling is consistent with the currently approved OTC analgesic/sleep-aid combination products. Does the Agency have any comments on the proposed Drug Facts labeling? (Section 7, Labeling)

FDA Preliminary Response:

These are preliminary comments. A full review of the proposed labeling will occur after the NDA is submitted and this review may generate additional comments.

Change the singular heading "Purpose" to the plural heading "Purposes" because the product ingredients have two distinct purposes and "Active ingredients" is plural.

To be consistent with other Aleve products, in "Ask a doctor or pharmacist before use if you are," the Aleve PM label should be changed from "under a doctor's care for (b) (4) [redacted]" to "under a doctor's care for any serious condition."

9. In the Tentative Final Nighttime Sleep-aid Monograph (June 13, 1978) the over-the-counter sleep aid indication was deemed inappropriate for children under the age of 12 due to concerns of masking underlying conditions. For children age 12 years and over, there are several over-the-counter products currently available with identical indications being sought in this application for children (Tylenol® PM, Advil® PM, Motrin® PM). As such, Bayer intends to include this age group on the Drug Facts Labeling. However, with several products already available on the market, the proposed product does not offer a significant clinically meaningful additional benefit for children over 12 years of age. Additionally, Bayer intends to provide market research data in the NDA to show that these combination products are not used extensively by children aged 12 to under 18. (b) (4)

[redacted]

[redacted]

FDA Preliminary Response:

We agree that you may request waivers and deferrals with justification, for our review at the appropriate time in your drug development program. The July 9, 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) changes the timeline for submission of a Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes.

Discussion:

Bayer inquired if they could submit their pediatric plan/pediatric assessment as part of their NDA. The Agency said that their proposal was acceptable.

10. In the NDA, Bayer plans to submit standardized datasets following the CDISC guidance for SDTM and ADaM datasets. In addition, Bayer will provide a data definition file, (in.pdf format or .xml format) and annotated case report forms (CRF) with information on variables included in the datasets. Does the Agency agree with this approach?

FDA Preliminary Response:

We strongly encourage you to send your submissions electronically. We recommend eCTD submissions using CDISC standards for study data and MedDRA coding for adverse events. General guidance and contact information is available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm>

11. In the course of development, several minor improvements were made to the HPLC method used in the Assay, Degradation Product, and Dissolution tests. As included in the background package, Bayer has evaluated these changes and has shown that data generated by the previous method and the proposed method are valid. Bayer concludes that there is no adverse impact on the overall stability assessment of the product and that we can utilize the revised method for future stability time points. Does the FDA agree with our conclusion? If not, would the FDA agree to a separate teleconference to address these improvements? (Section 9, Chemistry, Manufacturing & Controls)

FDA Preliminary Response:

According to the data you provided, the new revised version of the HPLC method, which includes changes in sample preparation (b) (4)

We have no objections to the use of the revised method for future stability points. However, comparison of the HPLC methods should be part of the proposed NDA, Sections P.2 (Pharmaceutical Development) and P.5 (Control of Drug Product).

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS/ SUMMARY OF KEY DISCUSSION POINTS

- Bayer will provide their scientific rationale that outlines why the totality of data from their drug development program adequately supports their application for their proposed drug product.
- For studies 14837 and 15881, Bayer will include the requested subgroup analyses as addendums to each final study report in Module 5 of the eCTD.
- To address the Agency's concern regarding next-day residual effects of diphenhydramine, Bayer will submit a comprehensive literature review (relevant to Bayer's proposed use) and targeted safety analysis based on postmarketing information (accidents or injuries) related to the administration of diphenhydramine at night for sleep.
- Bayer's pediatric plan/pediatric assessment can be submitted as part of their NDA.

5.0 ATTACHMENTS AND HANDOUTS

Attached are two options presented by Bayer for their proposed new tag lines on the PDP.

6.0 POST-MEETING ADDENDUM

In an e-mail sent October 5, 2012, Bayer requested initial feedback on a proposed tag line on the principal display panel of the product's outer carton. The two options presented were, [REDACTED] (b) (4) and "Sleep Aid + 12 Hour Pain Relieving Strength of Aleve".

Our preliminary response, pending full NDA review, is that "Sleep Aid + 12 Hour Pain Relieving Strength of Aleve" is preferable because it more accurately reflects the ingredients and indication than does [REDACTED] (b) (4)

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

/s/

ANDREA LEONARD SEGAL
11/05/2012

IND 103407
Meeting Minutes
Type A Meeting

Office of Drug Evaluation IV
Division of Nonprescription Clinical Evaluation

NDA 103407

MEETING MINUTES

Bayer HealthCare LLC Consumer Care
Attention: Leonard Baum, R.Ph.
Vice President, Regulatory Affairs
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962

Dear Mr. Baum:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aleve PM (naproxen sodium/ diphenhydramine HCl) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on Tuesday, September 7, 2010. The purpose of the meeting was to discuss the Agency's special protocol assessment of your protocol entitled, "A Multicenter, Randomized, Double-Blind, Parallel Group Trial Assessing the Efficacy of Naproxen Sodium and Diphenhydramine Combination in Postsurgical Dental Pain with Phase Advanced Sleep and Maximum Use Safety Experience."

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

If you have any questions, call James Lee, Regulatory Project Manager, at (301) 796-5283.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Division Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A

Meeting Category: Special Protocol Assessment

Meeting Date and Time: Tuesday, September 07, 2010
11:00 A.M. to 12:00 P.M., EDT

Meeting Location: Teleconference

Application Number: IND 103407

Product Name: Aleve PM (naproxen sodium/ diphenhydramine HCl) tablets

Indication: Pain Reliever/ Night time sleep-aid

Sponsor/Applicant Name: Bayer Healthcare LLC Consumer Care

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

Meeting Recorder: James Lee, PharmD
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation

Andrea Leonard-Segal, M.D. M.S., Director
Joel Schiffenbauer, M.D., Deputy Director
Lesley Furlong, M.D., Medical Team Leader
Christina Chang, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacologist/Toxicologist
Melissa Furness, Chief, Project Management Staff
Neel Patel, PharmD., Regulatory Project Manager
James Lee, PharmD., Regulatory Project Manager

Division of Neurology Products

Russell Katz, M.D., Division Director
Ronald Farkas, M.D., Ph.D., Medical Team Leader

Office of Translational Science
Angela Men, Ph.D., Supervisory Clinical Pharmacology
Sharon Yan, Ph.D., Statistical Reviewer

SPONSOR ATTENDEES

Wes Cetnarowski, M.D., Senior Vice President, Global Research and Development
Irene Laurora, Pharm.D., Vice President, Medical Affairs
Shirley Chen, Pharm.D., Director, Global Medical Affairs Analgesic
Yuan Wang, Pharm.D., Assicait Director, Medical Affairs OTC Brands
Leonard Baum, R.Ph., Vice President, Regulatory Affairs
Bill Walsh, R.Ph., Senior Associate Director, Regulatory Affairs
Gian Zisa, M.S., Senior Manager, Regulatory Affairs
Robert An, Ph.D., Senior Associate Director, Biostatistics

1. BACKGROUND

Bayer Healthcare LLC Consumer Care (Bayer) submitted a request to the FDA on March 5, 2010 for a Type A meeting to discuss the Agency's special protocol assessment of Bayer's protocol entitled, "A Multicenter, Randomized, Double-Blind, Parallel Group Trial Assessing the Efficacy of Naproxen Sodium and Diphenhydramine Combination in Postsurgical Dental Pain with Phase Advanced Sleep and Maximum Use Safety Experience." Following multidisciplinary review, the Agency disagreed with elements of the proposed study design and dose selection.

The Agency's preliminary responses to the questions contained in Bayer's March 5, 2010 meeting background package were provided to Bayer via e-mail on September 3, 2010. These preliminary responses appear in italics below. Following introductions, the meeting agenda consisted of a discussion regarding questions 2 and 4. For questions where no additional discussion is indicated, neither Bayer nor FDA raised any additional issues pertaining to these questions.

2. DISCUSSION

QUESTIONS:

1. Does the Agency agree with Bayer's rationale for estimation of sample size?

FDA Response to Question 1:

Sample size calculation with power of at least 90% for WASO and sleep latency is acceptable.

2. Does the Agency agree with Bayer's rationale

(b) (4)

FDA Response to Question 2:

(b) (4) *We feel that inclusion of a naproxen sodium 220 mg/DPH 25 mg treatment arm in this trial will provide additional clarity for dose response. The efficacy of the combination of naproxen sodium and diphenhydramine may differ from the*

efficacy of naproxen sodium and diphenhydramine used alone, thus allowing for consideration of a lower dose combination.

In addition, we think it is in your interest to include a naproxen sodium 220 mg/DPH 25 mg treatment arm. In order to support approval of the proposed combination product, your program needs to show that the combination product is adequately safe. Previous FDA findings for the safety of single ingredients would not be, of themselves, adequate to support safety of this novel combination product. As stated in the ICH E4 Guidance on dose response studies, “the highest tolerated dose or the dose with the largest effect... will not always be the optimal dose.” A lower dose combination product may be more appropriate due to safety considerations such as residual next-day effects on driving and acceptable safety profile in elderly consumers. Consistent with our current recommendations for sponsors developing prescription sedative-hypnotics, we strongly recommend that you specifically study next-day effects on driving.

Discussion:

Bayer inquired into the basis for the Agency’s concerns regarding the safety profile of diphenhydramine in this proposed combination, since the safety profile of diphenhydramine has been well characterized. Bayer noted that current diphenhydramine labels already include warning statements on operating machinery, including motor vehicles. In reply, FDA pointed to a general increase in awareness for the potential negative impact of sleep aids on next-day functioning. FDA clarified that, although a next-day driving study is not a requirement for approval, it would be useful to have such data to make labeling more informative and to further quantify the effect. Bayer expressed an understanding of FDA’s concerns and stated that they intend to try to address these concerns in the NDA.

Bayer also agreed to consider the Agency’s recommendation to add a treatment arm to assess naproxen sodium 220 mg/diphenhydramine 25 mg. However, given the number of existing treatment arms in this trial and potential decision points already involved, Bayer will consider including another trial in the development program to assess the lower-dose combination.

3. Does the Agency agree with the revised assumptions for naproxen sodium 440 mg/DPH 50 mg to be considered an appropriate dose?

FDA Response to Question 3:

Your use of ‘equal’ and ‘greater/less than’ symbols is problematic because these notations do not account for the clinical meaningfulness of differences; a lower dose might be appropriate due to safety considerations if differences (including nominal ‘less than’ findings) are not clinically meaningful.

We also note that you have not covered all possible outcomes with your dose selection algorithm. It is not clear how you will choose the appropriate dose if one dose is better than another on one endpoint, but no different (or worse) on the other endpoint.

We reiterate our previous comment that both efficacy and safety considerations are important in dosing selection. You should choose the dose for marketing based on review of all available data. See our response to question 2 above.

4. Does the Agency agree with the revised proposed data handling methodology for WASO and sleep latency in subjects who require rescue medication?

FDA Response to Question 4:

The handling methodology only addressed the possible outcome that the DPH alone group would have a larger proportion of subjects taking rescue medication. Bayer needs to also address the possibility that the naproxen sodium group may have a larger proportion of subjects taking rescue medication than the combination group. We reiterate that the study results could be difficult to interpret if a large number of subjects take rescue medication.

Discussion:

Bayer provided follow-up responses to the Agency's preliminary comment via electronic mail on September 7, 2010 (see attachment). In response to Bayer's revised data handling methodology, FDA stated that Bayer's proposals for both endpoints were acceptable.

5. Does the Agency agree with the revised proposed secondary object in sleep parameters?

FDA Response to Question 5:

The absence of a clock/watch in the room does not appear relevant to the measurement of subjective sleep latency and subjective WASO; these are subjective measures, and do not depend on the patient reading the time on a clock/watch.

While subjective measures may be less accurate than objective measures, they provide information about the clinical meaningfulness of objective findings, and should therefore be measured in the study. The secondary subjective sleep assessments you outline in the protocol do not appear to provide the same information as subjective sleep latency and subjective WASO. The Karolinska Sleep Diary includes questions about ease of falling asleep and about premature awakening, but the questions appear to represent more complex concepts, with less certain interpretation, than direct questions about subjective sleep latency and WASO. We are, however, willing to consider additional arguments that your proposed endpoints are acceptable.

6. Does the Agency agree with the proposed treatment arms and sample size for the maximum use safety assessment study?

FDA Response to Question 6:

The treatment arms and sample size are acceptable if no unexpected issues arise during the development program. We note that your active treatment arm in the safety study uses the maximum dose that you will study for efficacy. If you select a lower dose for marketing, your

safety study may define a safety profile that is less favorable than the safety profile for the to-be-marketed dose. In your safety study, you should enroll a population that includes older subjects and is reasonably representative of the expected target population of Aleve PM.

See also our responses to questions 2 and 3 above.

7. Does the Agency agree that this revised approach is adequate to address multiple dose maximum use safety assessment to support the data requested and the maximum proposed label usage of 10 days?

FDA Response to Question 7:

We recommend that you submit the detailed protocol for Agency review and comment. At this time, the need for additional studies, including safety assessment in accordance to ICH E1A guidelines, to address safety issues that might arise during the development program cannot be excluded.

8. [REDACTED] (b) (4)

FDA Response to Question 8:

[REDACTED] (b) (4)

[REDACTED]

9. Bayer will provide a rationale for extrapolating the safety and efficacy data from adults and adolescents ≥ 16 years old to children 12 to 15 years of age and will also address the requirements of the Pediatric Research Equity Act for Aleve PM at the time of NDA submission

Does the Agency agree with this approach?

FDA Response to Question 9:

Your approach to address the PREA requirements appears acceptable. We recommend that the pediatric plan be presented as early as possible. Whether the final labeling includes children 12 to 15 years of age will be determined when the Agency has completed review of pediatric data from the pivotal trial as well as your rationale for data extrapolation from adults and adolescents aged 16 and older.

10. Does the Agency consider a [REDACTED] ^{(b) (4)} administration where an unblinded pharmacist or nurse administers the study medication acceptable?

FDA Response to Question 10:

No, we do not. The investigational products should be over-encapsulated to preserve blinding and minimize potential bias; use of drug product that preserves blinding appears feasible. You will need to provide compelling reasons to deviate from this design.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

4.0 SUMMARY OF KEY DISCUSSION POINTS:

1. Bayer will consider the addition of a naproxen sodium 220 mg/diphenhydramine 25 mg treatment arm.
2. Agency confirmed that a driving study would be useful but not required.
3. Agency confirmed that the revised data handling methodology is acceptable. (See attached handout).

5.0 ATTACHMENTS AND HANDOUTS

The following information is a response from Bayer regarding the Agency's preliminary comments to question #4. The information was received as an attachment to an electronic mail on September 7, 2010, at 9:22 AM EDT.

Bayer's Response to Question #4

According to the Agency's comment, we are proposing the following analyses for WASO to be consistent with those proposed for sleep latency:

Based on the data from the pilot study, the proportions of subjects requiring the rescue medication are similar to each other among Naproxen sodium/DPH combinations and Naproxen sodium alone. In order to assess the robustness of the efficacy results, the following sensitivity analyses will be performed to collaborate the primary analysis on the ITT population for WASO (the primary interest of treatment comparisons of Naproxen sodium/DPH combinations vs. Naproxen sodium alone):

- Sensitivity analysis will be performed on the population excluding subjects who have taken rescue medication;

- If there is a larger proportion of subjects requiring rescue in the Naproxen sodium alone group, randomly select the subjects in the Naproxen sodium alone group that is equal to the proportion of subjects who have taken rescue medication for the other comparison group. Selected subjects in the Naproxen sodium alone group and all rescued subjects in the comparison group will be imputed as originally proposed and the deselected subjects in the Naproxen sodium alone group will be imputed using the median value of those who have NOT taken rescue medication in the combined groups of comparison. The seed for the random selection will be 145929879;
- If there is a larger proportion of subjects requiring rescue in the Naproxen sodium alone group, randomly select the subjects in the Naproxen sodium alone group that is equal to the proportion of subjects who have taken rescue medication for the other comparison group. Selected subjects in the Naproxen sodium alone group and all rescued subjects in the comparison group will be imputed as originally proposed and the deselected subjects in the Naproxen sodium alone group will be excluded from the sensitivity analysis. The seed for the random selection will be 256457239;

The efficacy evidence will be based on the totality of the primary analysis on the ITT population and the supportive analyses as specified above.

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/s/

ANDREA LEONARD SEGAL
09/24/2010

IND 103407
Meeting Minutes
Type A Meeting

Office of Drug Evaluation IV
Division of Nonprescription Clinical Evaluation

NDA 103407

MEETING MINUTES

Bayer HealthCare LLC Consumer Care
Attention: Leonard Baum, R.Ph.
Vice President, Regulatory Affairs
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962

Dear Mr. Baum:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aleve PM (naproxen sodium/ diphenhydramine HCl) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on Tuesday, September 7, 2010. The purpose of the meeting was to discuss the Agency's special protocol assessment of your protocol entitled, "A Multicenter, Randomized, Double-Blind, Parallel Group Trial Assessing the Efficacy of Naproxen Sodium and Diphenhydramine Combination in Postsurgical Dental Pain with Phase Advanced Sleep and Maximum Use Safety Experience."

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

If you have any questions, call James Lee, Regulatory Project Manager, at (301) 796-5283.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Division Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A

Meeting Category: Special Protocol Assessment

Meeting Date and Time: Tuesday, September 07, 2010
11:00 A.M. to 12:00 P.M., EDT

Meeting Location: Teleconference

Application Number: IND 103407

Product Name: Aleve PM (naproxen sodium/ diphenhydramine HCl) tablets

Indication: Pain Reliever/ Night time sleep-aid

Sponsor/Applicant Name: Bayer Healthcare LLC Consumer Care

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

Meeting Recorder: James Lee, PharmD
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation

Andrea Leonard-Segal, M.D. M.S., Director
Joel Schiffenbauer, M.D., Deputy Director
Lesley Furlong, M.D., Medical Team Leader
Christina Chang, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacologist/Toxicologist
Melissa Furness, Chief, Project Management Staff
Neel Patel, PharmD., Regulatory Project Manager
James Lee, PharmD., Regulatory Project Manager

Division of Neurology Products

Russell Katz, M.D., Division Director
Ronald Farkas, M.D., Ph.D., Medical Team Leader

Office of Translational Science
Angela Men, Ph.D., Supervisory Clinical Pharmacology
Sharon Yan, Ph.D., Statistical Reviewer

SPONSOR ATTENDEES

Wes Cetnarowski, M.D., Senior Vice President, Global Research and Development
Irene Laurora, Pharm.D., Vice President, Medical Affairs
Shirley Chen, Pharm.D., Director, Global Medical Affairs Analgesic
Yuan Wang, Pharm.D., Assicait Director, Medical Affairs OTC Brands
Leonard Baum, R.Ph., Vice President, Regulatory Affairs
Bill Walsh, R.Ph., Senior Associate Director, Regulatory Affairs
Gian Zisa, M.S., Senior Manager, Regulatory Affairs
Robert An, Ph.D., Senior Associate Director, Biostatistics

1. BACKGROUND

Bayer Healthcare LLC Consumer Care (Bayer) submitted a request to the FDA on March 5, 2010 for a Type A meeting to discuss the Agency's special protocol assessment of Bayer's protocol entitled, "A Multicenter, Randomized, Double-Blind, Parallel Group Trial Assessing the Efficacy of Naproxen Sodium and Diphenhydramine Combination in Postsurgical Dental Pain with Phase Advanced Sleep and Maximum Use Safety Experience." Following multidisciplinary review, the Agency disagreed with elements of the proposed study design and dose selection.

The Agency's preliminary responses to the questions contained in Bayer's March 5, 2010 meeting background package were provided to Bayer via e-mail on September 3, 2010. These preliminary responses appear in italics below. Following introductions, the meeting agenda consisted of a discussion regarding questions 2 and 4. For questions where no additional discussion is indicated, neither Bayer nor FDA raised any additional issues pertaining to these questions.

2. DISCUSSION

QUESTIONS:

1. Does the Agency agree with Bayer's rationale for estimation of sample size?

FDA Response to Question 1:

Sample size calculation with power of at least 90% for WASO and sleep latency is acceptable.

2. Does the Agency agree with Bayer's rationale

(b) (4)

FDA Response to Question 2:

(b) (4) *We feel that inclusion of a naproxen sodium 220 mg/DPH 25 mg treatment arm in this trial will provide additional clarity for dose response. The efficacy of the combination of naproxen sodium and diphenhydramine may differ from the*

efficacy of naproxen sodium and diphenhydramine used alone, thus allowing for consideration of a lower dose combination.

In addition, we think it is in your interest to include a naproxen sodium 220 mg/DPH 25 mg treatment arm. In order to support approval of the proposed combination product, your program needs to show that the combination product is adequately safe. Previous FDA findings for the safety of single ingredients would not be, of themselves, adequate to support safety of this novel combination product. As stated in the ICH E4 Guidance on dose response studies, “the highest tolerated dose or the dose with the largest effect... will not always be the optimal dose.” A lower dose combination product may be more appropriate due to safety considerations such as residual next-day effects on driving and acceptable safety profile in elderly consumers. Consistent with our current recommendations for sponsors developing prescription sedative-hypnotics, we strongly recommend that you specifically study next-day effects on driving.

Discussion:

Bayer inquired into the basis for the Agency’s concerns regarding the safety profile of diphenhydramine in this proposed combination, since the safety profile of diphenhydramine has been well characterized. Bayer noted that current diphenhydramine labels already include warning statements on operating machinery, including motor vehicles. In reply, FDA pointed to a general increase in awareness for the potential negative impact of sleep aids on next-day functioning. FDA clarified that, although a next-day driving study is not a requirement for approval, it would be useful to have such data to make labeling more informative and to further quantify the effect. Bayer expressed an understanding of FDA’s concerns and stated that they intend to try to address these concerns in the NDA.

Bayer also agreed to consider the Agency’s recommendation to add a treatment arm to assess naproxen sodium 220 mg/diphenhydramine 25 mg. However, given the number of existing treatment arms in this trial and potential decision points already involved, Bayer will consider including another trial in the development program to assess the lower-dose combination.

3. Does the Agency agree with the revised assumptions for naproxen sodium 440 mg/DPH 50 mg to be considered an appropriate dose?

FDA Response to Question 3:

Your use of ‘equal’ and ‘greater/less than’ symbols is problematic because these notations do not account for the clinical meaningfulness of differences; a lower dose might be appropriate due to safety considerations if differences (including nominal ‘less than’ findings) are not clinically meaningful.

We also note that you have not covered all possible outcomes with your dose selection algorithm. It is not clear how you will choose the appropriate dose if one dose is better than another on one endpoint, but no different (or worse) on the other endpoint.

We reiterate our previous comment that both efficacy and safety considerations are important in dosing selection. You should choose the dose for marketing based on review of all available data. See our response to question 2 above.

4. Does the Agency agree with the revised proposed data handling methodology for WASO and sleep latency in subjects who require rescue medication?

FDA Response to Question 4:

The handling methodology only addressed the possible outcome that the DPH alone group would have a larger proportion of subjects taking rescue medication. Bayer needs to also address the possibility that the naproxen sodium group may have a larger proportion of subjects taking rescue medication than the combination group. We reiterate that the study results could be difficult to interpret if a large number of subjects take rescue medication.

Discussion:

Bayer provided follow-up responses to the Agency's preliminary comment via electronic mail on September 7, 2010 (see attachment). In response to Bayer's revised data handling methodology, FDA stated that Bayer's proposals for both endpoints were acceptable.

5. Does the Agency agree with the revised proposed secondary object in sleep parameters?

FDA Response to Question 5:

The absence of a clock/watch in the room does not appear relevant to the measurement of subjective sleep latency and subjective WASO; these are subjective measures, and do not depend on the patient reading the time on a clock/watch.

While subjective measures may be less accurate than objective measures, they provide information about the clinical meaningfulness of objective findings, and should therefore be measured in the study. The secondary subjective sleep assessments you outline in the protocol do not appear to provide the same information as subjective sleep latency and subjective WASO. The Karolinska Sleep Diary includes questions about ease of falling asleep and about premature awakening, but the questions appear to represent more complex concepts, with less certain interpretation, than direct questions about subjective sleep latency and WASO. We are, however, willing to consider additional arguments that your proposed endpoints are acceptable.

6. Does the Agency agree with the proposed treatment arms and sample size for the maximum use safety assessment study?

FDA Response to Question 6:

The treatment arms and sample size are acceptable if no unexpected issues arise during the development program. We note that your active treatment arm in the safety study uses the maximum dose that you will study for efficacy. If you select a lower dose for marketing, your

safety study may define a safety profile that is less favorable than the safety profile for the to-be-marketed dose. In your safety study, you should enroll a population that includes older subjects and is reasonably representative of the expected target population of Aleve PM.

See also our responses to questions 2 and 3 above.

7. Does the Agency agree that this revised approach is adequate to address multiple dose maximum use safety assessment to support the data requested and the maximum proposed label usage of 10 days?

FDA Response to Question 7:

We recommend that you submit the detailed protocol for Agency review and comment. At this time, the need for additional studies, including safety assessment in accordance to ICH E1A guidelines, to address safety issues that might arise during the development program cannot be excluded.

8. [REDACTED] (b) (4)

FDA Response to Question 8:

[REDACTED] (b) (4)

[REDACTED]

9. Bayer will provide a rationale for extrapolating the safety and efficacy data from adults and adolescents \geq 16 years old to children 12 to 15 years of age and will also address the requirements of the Pediatric Research Equity Act for Aleve PM at the time of NDA submission

Does the Agency agree with this approach?

FDA Response to Question 9:

Your approach to address the PREA requirements appears acceptable. We recommend that the pediatric plan be presented as early as possible. Whether the final labeling includes children 12 to 15 years of age will be determined when the Agency has completed review of pediatric data from the pivotal trial as well as your rationale for data extrapolation from adults and adolescents aged 16 and older.

10. Does the Agency consider a [REDACTED] ^{(b) (4)} administration where an unblinded pharmacist or nurse administers the study medication acceptable?

FDA Response to Question 10:

No, we do not. The investigational products should be over-encapsulated to preserve blinding and minimize potential bias; use of drug product that preserves blinding appears feasible. You will need to provide compelling reasons to deviate from this design.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

4.0 SUMMARY OF KEY DISCUSSION POINTS:

1. Bayer will consider the addition of a naproxen sodium 220 mg/diphenhydramine 25 mg treatment arm.
2. Agency confirmed that a driving study would be useful but not required.
3. Agency confirmed that the revised data handling methodology is acceptable. (See attached handout).

5.0 ATTACHMENTS AND HANDOUTS

The following information is a response from Bayer regarding the Agency's preliminary comments to question #4. The information was received as an attachment to an electronic mail on September 7, 2010, at 9:22 AM EDT.

Bayer's Response to Question #4

According to the Agency's comment, we are proposing the following analyses for WASO to be consistent with those proposed for sleep latency:

Based on the data from the pilot study, the proportions of subjects requiring the rescue medication are similar to each other among Naproxen sodium/DPH combinations and Naproxen sodium alone. In order to assess the robustness of the efficacy results, the following sensitivity analyses will be performed to collaborate the primary analysis on the ITT population for WASO (the primary interest of treatment comparisons of Naproxen sodium/DPH combinations vs. Naproxen sodium alone):

- Sensitivity analysis will be performed on the population excluding subjects who have taken rescue medication;

- If there is a larger proportion of subjects requiring rescue in the Naproxen sodium alone group, randomly select the subjects in the Naproxen sodium alone group that is equal to the proportion of subjects who have taken rescue medication for the other comparison group. Selected subjects in the Naproxen sodium alone group and all rescued subjects in the comparison group will be imputed as originally proposed and the deselected subjects in the Naproxen sodium alone group will be imputed using the median value of those who have NOT taken rescue medication in the combined groups of comparison. The seed for the random selection will be 145929879;
- If there is a larger proportion of subjects requiring rescue in the Naproxen sodium alone group, randomly select the subjects in the Naproxen sodium alone group that is equal to the proportion of subjects who have taken rescue medication for the other comparison group. Selected subjects in the Naproxen sodium alone group and all rescued subjects in the comparison group will be imputed as originally proposed and the deselected subjects in the Naproxen sodium alone group will be excluded from the sensitivity analysis. The seed for the random selection will be 256457239;

The efficacy evidence will be based on the totality of the primary analysis on the ITT population and the supportive analyses as specified above.

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/s/

ANDREA LEONARD SEGAL
09/24/2010