CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203697Orig1s000

OTHER REVIEW(S)

3rd Addendum Labeling Review for PL 2200 Aspirin Capsules

SUBMISSION DATES:	January 10, 2013
NDA/SUBMISSION TYPE:	203697 (PA)
ACTIVE INGREDIENTS:	Aspirin 325 mg
DOSAGE FORMS:	Capsule, liquid-filled
SPONSOR:	PLx Pharma Inc. 8285 El Rio Street, Suite 130 Houston, Texas 77054 Jason E. Moore Vice President (713) 842-1249
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD

I. BACKGROUND

FDA provided the following labeling comments on January 10, 2013 and the sponsor responded on January 10, 2013 with revised labels.

Submit revised labels so that the statement of identity on the principal display panel (PDP) has "Capsules" as the dosage form rather than "(b) (4)". This revision should be made to all SKUs (carton, bottle and blister labels). The net quantity of contents should still state "XX Liquid Filled Capsules" on the PDP.

Also, on the Drug Facts label for all SKUs, under "***Active ingredient***", change (b) (4) to "(in each capsule)".

II. REVIEWER'S COMMENTS

A. PDP on all SKUs - Dosage form in the statement of identity

The dosage form listed in the statement of identity has been revised from "(b) (4) (b) (4)" to "Capsules" on the PDP for all SKUs. This change is acceptable.

B. Drug Facts Label - Active ingredient

Under ***Active ingredient***, the dosage form has been changed from "(b) (4)" to "(in each capsule)". The sponsor should submit revised labeling with this change.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Aspirin capsules carton and immediate container (bottle and blister card) labels and request final printed labeling.

Request that the sponsor submit final printed labeling (FPL) for Aspirin capsules identical to: 7-, 28-, 30- and 120-count carton and immediate container (7-count blister and 30- and 120-count bottle) labels submitted on January 10, 2013, when available.

IV. SUBMITTED LABELING

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

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

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/s/

KATHLEEN M PHELAN
01/14/2013
primary author is Elaine Abraham

STEVEN A ADAH
01/14/2013

2nd Addendum Labeling Review for PL 2200 Aspirin Capsules

SUBMISSION DATES:	January 7, 2013
NDA/SUBMISSION TYPE:	203697 (PA)
ACTIVE INGREDIENTS:	Aspirin 325 mg
DOSAGE FORMS:	Capsule, liquid-filled
SPONSOR:	PLx Pharma Inc. 8285 El Rio Street, Suite 130 Houston, Texas 77054 Jason E. Moore Vice President (713) 842-1249
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD

I. BACKGROUND

FDA provided the following labeling comments on January 3, 2013 and the sponsor responded on January 7, 2013 with revised labels.

Principal Display Panel (PDP) on all SKUs

- **Trade name**
  Submit revised labels without a trade name and using the established name for the drug product.
- (b) (4) [redacted] (b) (4) [redacted].

- (b) (4)
  Promotional language of this nature is not typically allowed on products approved under an NDA. We are not aware of any products approved under an NDA that have this type of language on the PDP. We stand by our original objection to (b) (4) as implying a superiority claim when compared to an NDA-approved product that does not carry such language. The labels submitted that have the promotional language removed have been used as the basis for this labeling review.

Drug Facts Label on all SKUs

- **Inactive ingredients**
  Under **Inactive ingredients**, the period at the end of the inactive ingredient list should be removed (see Drug Facts format in examples provided under 21 CFR 201.66(d)).

Outer Carton Drug Facts Label (7- and 28-count cartons)

- **Uses**
  Under **Uses**, as the 7- and 28-count cartons do not meet the requirements for the modified labeling format under 21 CFR 201.66 (d)(10), bullets must be aligned (See 21 CFR 201.66(d)(4).) The statements [bullet] toothache and [bullet] minor pain of arthritis should be aligned.

Immediate Container Label (7-count blister card)

- With the revision of the blister card, there is now ample space to include more information and exceed the minimum requirements for the immediate container listed under 21 CFR 201.10(h)(2)(i). The name and place (city, state and zip code) of the manufacturer, packer, or distributor of the drug should be placed on each individual blister (see Section 502(b) of the Federal Food, Drug and Cosmetic Act).
- **Reye's syndrome warning**
  In the Reye's syndrome warning, the words "because these" in the phrase "…because these symptoms could be an early sign of Reye's syndrome…" run together and should be separated by a space. (See 21 CFR 201.314(h)(1).)

Submitted Labeling	Representative of Following SKUs
30-count bottle and carton	N/A
120-count bottle and carton	N/A
7-count blister card	N/A
7-count blister carton	N/A
28-count blister carton	N/A

II. REVIEWER'S COMMENTS

A. Outer Carton Label Outside Drug Facts – PDP on all SKUs

1. **Trade name**
   The trade name previously submitted on the labels, (b) (4), was found unacceptable by DMEPA. The revised labels use the established name "Aspirin" as the trade name for the product. Following approval and prior to marketing, the sponsor plans to propose a new proprietary name for review. The labels use the active ingredient "Aspirin" as the trade name and established name. This part of the PDP is acceptable.
2. **Dosage form in statement of identity**
   The dosage form listed in the statement of identity is (b) (4)" rather than "Capsules". This issue was brought up by the review team (DNCE, ONDQA, DMEPA) on January 9, 2013. The team agrees that the dosage form should be changed to "Capsules". The sponsor should submit revised labeling with this change.
3. (b) (4)
   The (b) (4) have been removed from the label and is acceptable.
4. **Promotional language on PDP** (b) (4)
   The words (b) (4) have been removed from the label. The PDP is acceptable.

B. Drug Facts Label

1. **Active ingredient**
   Under ***Active ingredient***, the dose is listed (b) (4) In line with changing the dosage form in the statement of identity, the dosage form here should be changed from (b) (4) to "(in each capsule)". The sponsor should submit revised labeling with this change.
2. **Uses**
   Under ***Uses***, the statements [bullet] toothache and [bullet] minor pain of arthritis have been aligned on the 7- and 28-count cartons to comply with 21 CFR 201.66(d)(4). This revision is acceptable.
3. **Inactive ingredients for all SKUs**
   Under ***Inactive ingredients*****,** the period at the end of the inactive ingredient list has been removed to comply with 21 CFR 201.66(d).

C. Immediate Container labels (7-count blister card)

1. The name and place of the manufacturer has been included on each individual blister to comply with Section 502(b) of the Act and is acceptable.
2. **Reye's syndrome warning**
   Under the Reye's syndrome warning, the words "because these" in the phrase "…because these symptoms could be an early sign of Reye's syndrome…" have been separated by a space so they no longer run together in accordance with 21 CFR 201.314(h)(1).

III. RECOMMENDATIONS

The labeling deficiencies listed below should be communicated to the sponsor. Labeling should be revised and resubmitted for our review.

1. Submit revised labels so that the statement of identity on the principal display panel (PDP) has "Capsules" as the dosage form rather than (b) (4) This revision should be made to all SKUs (carton, bottle and blister labels). The net quantity of contents should still state "XX Liquid Filled Capsules" on the PDP.
2. On the Drug Facts label for all SKUs, under "Active ingredient", change "((b) (4) " to "(in each capsule)".

IV. SUBMITTED LABELING

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

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/s/

ELAINE E ABRAHAM
01/11/2013

STEVEN A ADAH
01/11/2013

Addendum Labeling Review for PL 2200 Aspirin Capsules

SUBMISSION DATES:	December 17, 2012
NDA/SUBMISSION TYPE:	203697 (PA)
ACTIVE INGREDIENTS:	Aspirin 325 mg
DOSAGE FORMS:	Capsule, liquid-filled
SPONSOR:	PLx Pharma Inc. 8285 El Rio Street, Suite 130 Houston, Texas 77054 Jason E. Moore Vice President (713) 842-1249
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD

I. BACKGROUND

FDA provided labeling comments on December 10, 2012 and the sponsor responded on December 17, 2012 with revised labels. The labels use the trade name (b) (4). Two sets of labels were included – one which had all principal display panel (PDP) changes recommended by FDA and one which included the words (b) (4) and the (b) (4), issues that the sponsor disagreed with FDA's position.

Submitted Labeling	Representative of Following SKUs
30-count bottle and carton	N/A
120-count bottle and carton	N/A
7-count blister card	N/A
7-count blister carton	N/A
28-count blister carton	N/A

II. REVIEWER'S COMMENTS

A. All SKUs

i. Outer Carton Label Outside Drug Facts

a. Principal Display Panel (PDP)

1. **Trade name**

The labels submitted on December 17, 2012, which include the trade name (b) (4) are reviewed here. DMEPA informed us that they find the trade name (b) (4) unacceptable (review pending). The sponsor should submit revised labels without a trade name and using the established name for the product.

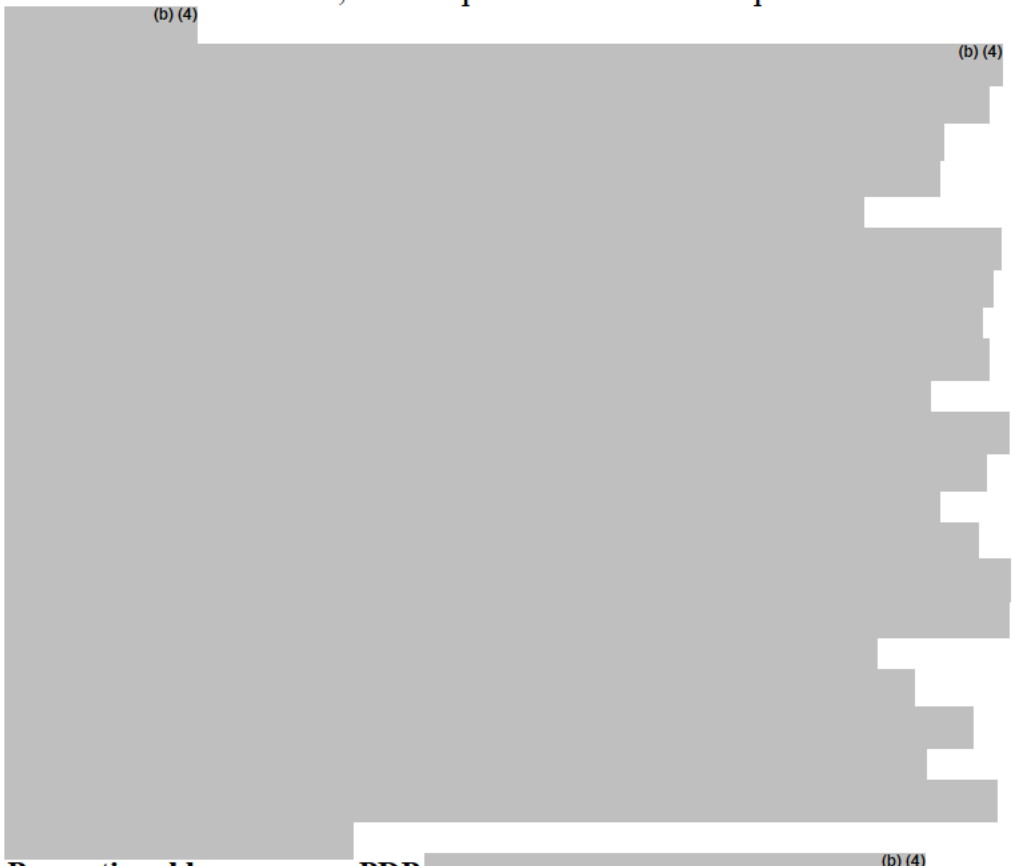
2. **Statement of Identity**

The statement of identity has been revised to follow the standard format according to 21 CFR 201.61(b). Also, the statement of identity has been enlarged to comply with 21 CFR 201.61(c). The designation "(NSAID)" has been added to the statement of identity to comply with 21 CFR 201.326(a)(2)(i). The statement of identity is acceptable.

3. **Liquid Filled Capsules**

The sponsor has included "Liquid Filled Capsules" in the net quantity of contents as recommended, and this part of the PDP is acceptable.

4. (b) (4)



5. **Promotional language on PDP** (b) (4)

(a) (b) (4)

Our December 10, 2012 comments to the sponsor stated that the words (b) (4) should be removed from the PDP because they are

considered promotional language that may be misleading by implying a superiority claim [redacted]. The sponsor objected to the removal of the words [redacted] but nonetheless provided labels with this language removed.

The sponsor presents the following points:

[redacted]

[redacted] (b) (4)

The labels submitted by the sponsor that have the words [redacted] (b) (4) removed have been used as the basis for this labeling review.

(b) [redacted] (b) (4)

The word [redacted] (b) (4) has been removed from the PDP and this revision is acceptable.

ii. Side Panels

a. Statement of Identity

The statement of identity on the side panels has been revised to agree with the statement of identity on the PDP and is acceptable.

b. Tamper evident statement (30-count and 120-count cartons)

According to 21 CFR 211.132(c)(2), if the tamper-evident feature uses an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture), the identifying characteristic should be included in the tamper-evident label statement. The tamper evident statement has been revised to read "Tamper evident: Do not use if the imprinted safety seal with repeated text 'Sealed for your protection' under cap is missing or broken". This revision is acceptable.

iii. Outer Carton Drug Facts Label for all SKUs

a. Uses

As requested in our December 10, 2012 comments, a bullet has been inserted before the phrase "for the temporary relief of minor aches…". Also for clarity, "temporarily reduces fever" has been placed on a separate line for the 7- and 28-count cartons. These changes are acceptable. As the 7- and 28-count cartons do not meet the requirements for the modified labeling format under 21 CFR 201.66 (d)(10), bullets must be aligned (See 21 CFR 201.66(d)(4).) The statements [bullet] toothache and [bullet] minor pain of arthritis should be aligned.

b. Warnings

1. Reye's syndrome

The word "should" has been added to the statement, "Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product." (See 21 CFR 201.314(h)(1).) This warning is acceptable.

2. Stomach bleeding warning

The word "stomach" has been added to in the statement "This product contains an NSAID, which may cause severe stomach bleeding." (See 21 CFR 201.326(a)(2)(iii)(A).) This warning is acceptable.

3. **Ask a doctor before use if**
   The word "a" has been removed from the statement "you have high blood pressure, heart disease, liver cirrhosis, or kidney disease" as requested so that now it agrees with 21 CFR 201.326(a)(2)(iii)(B). This warning is acceptable.
4. **Ask a doctor or pharmacist before use**
   The first two bullets were deleted as requested. This warning is acceptable.
5. **Stop use and ask a doctor if**
   Two statements were revised to be consistent with the NSAID template (67 FR 54150) which presents Drug Facts format for the IAAA warnings (53 FR 46256):
   [redacted] (b) (4) was revised to
   "[bullet] fever get worse or lasts for more than 3 days"
   [redacted] (b) (4) was revised to
   "[bullet] redness or swelling is present in the painful area"
   The statement [redacted] (b) (4) is not required and was removed. This warning is acceptable.
6. **Keep out of reach of children (30- and 120-count cartons)**
   This warning was added to the 30- and 120-count carton Drug Facts labels as required under 21 CFR 201.314(a) and 21 CFR 330.1(g). This warning is acceptable.

c. Directions
The phrase "while symptoms persist" was added after "…every 6 hours". (See 53 FR 46257 and NSAID template [67 FR 54150].) The directions are acceptable.

d. Other information

1. **Storage conditions**
   The "°" (degree) symbol was added to the statements showing storage temperatures. This part of the label is acceptable.
2. **Tamper evident statement (7- and 28-count cartons)**
   The sponsor revised the tamper evident statement to comply with 21 CFR 211.132(c)(1)(i) and identify all tamper evident features. The tamper evident statement is acceptable on these SKUs.
3. **Bullet alignment (7- and 28-count cartons)**
   The statement "[bullet] do not use if blue band…" was moved to the next line and vertically aligned with other bulleted statements to comply with 21 CFR 201.66(d)(4). This is acceptable.

e. Inactive ingredients
The wording [redacted] (b) (4)" was removed and all inactive ingredients were listed alphabetically (See 21 CFR 201.66(c)(8).) However, the period at the end of the inactive ingredient list should be removed (see Drug Facts format in examples provided under 21 CFR 201.66(d)).

f. Drug Facts Specifications

1. **(7- and 28-count cartons)** The "**Do not use**" subheading was changed to a type size consistent with all other subheadings in accordance with 21 CFR 201.66(d) and is acceptable.

2. **(7- and 28-count cartons)** A hairline was added following the statement "[bullet] you have asthma" under the subheading "**Ask a doctor before use**" and preceding the heading "**Ask a doctor or pharmacist before use if you are**" in accordance with 21 CFR 201.66(d)(8) and is acceptable.

iv. Immediate Container labels

a. 30- and 120-count bottle labels

1. **PDP**
   The PDP on the bottles was revised to agree with the recommendations made for the carton PDP and is acceptable.
2. **Drug Facts**
   Drug Facts revisions made to the carton were also made to the bottle labels and are acceptable.
3. Annotated specifications were submitted for the 30- and 120-count bottles and are acceptable.

b. 7-count blister card

1. (b) (4) The sponsor has placed the minimum items required for the immediate container as listed under 21 CFR 201.10(h)(2)(i). However, the revised blister has ample room for the name and place of the manufacturer, packer, or distributor of the drug (see Section 502(b) of the Act). The name of the manufacturer is included in the upper left part of the blister, but the place (city, state and zip code) is missing. As there is room, this information (name and place of manufacturer) should be placed on each individual blister.
2. **NSAID identification**
   "(NSAID)" was added as part of the established name to comply with 21 CFR 201.326(a)(2)(i)(B) and is acceptable.
3. **Stomach bleeding warning**
   The stomach bleeding warning was added to the blister card as required by 21 CFR 201.326(a)(2)(iii)(A) and is acceptable.
4. **Reye's syndrome warning**
   The Reye's syndrome warning was added to the blister card as required by 21 CFR 201.314(h)(1) and (2). The words "because these" in the phrase "…because these symptoms could be an early sign of Reye's syndrome…" run together and should be separated by a space. (See 21 CFR 201.314(h)(1).)

III. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the labeling deficiencies listed below.

Principal Display Panel (PDP) on all SKUs

- **Trade name**
  In case the trade name is not found acceptable, submit revised labels without a trade name and using the established name for the drug product.

- (b) (4) (b) (4) .
- (b) (4) Promotional language of this nature is not typically allowed on products approved under an NDA. We are not aware of any products approved under an NDA that have this type of language on the PDP. We stand by our original objection to (b) (4) as implying a superiority claim when compared to an NDA-approved product that does not carry such language. The labels submitted that have the promotional language removed have been used as the basis for this labeling review.

Drug Facts Label on all SKUs

- **Inactive ingredients**
  Under **Inactive ingredients**, the period at the end of the inactive ingredient list should be removed (see Drug Facts format in examples provided under 21 CFR 201.66(d)).

Outer Carton Drug Facts Label (7- and 28-count cartons)

- **Uses**
  Under **Uses**, as the 7- and 28-count cartons do not meet the requirements for the modified labeling format under 21 CFR 201.66 (d)(10), bullets must be aligned (See 21 CFR 201.66(d)(4).) The statements [bullet] toothache and [bullet] minor pain of arthritis should be aligned.

Immediate Container Label (7-count blister card)

- With the revision of the blister card, there is now ample space to include more information and exceed the minimum requirements for the immediate container listed under 21 CFR 201.10(h)(2)(i). The name and place (city, state and zip code) of the manufacturer, packer, or distributor of the drug should be placed on each individual blister (see Section 502(b) of the Federal Food, Drug and Cosmetic Act).
- **Reye's syndrome warning**
  In the Reye's syndrome warning, the words "because these" in the phrase "…because these symptoms could be an early sign of Reye's syndrome…" run together and should be separated by a space. (See 21 CFR 201.314(h)(1).)

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

IV. SUBMITTED LABELING

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

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/s/

ELAINE E ABRAHAM
01/02/2013

STEVEN A ADAH
01/02/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 203697	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Aspirin Dosage Form: capsule, liquid filled Strengths: 325 mg		
Applicant: PLx Pharma Inc.		
Date of Receipt: 03/14/2012		
PDUFA Goal Date: 01/14/2013	Action Goal Date (if different):	
Proposed Indication(s): For temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, premenstrual and menstrual cramps; for temporarily reducing fever.		

GENERAL INFORMATION

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

YES ☐ NO ☒

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

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	Pharmacokinetic, safety and efficacy data

*each source of information should be listed on separate rows

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

The Sponsor relies on the published literature to support the efficacy and safety of the proposed drug, as the IAAA monograph in which aspirin is marketed remains in tentative final monograph status. Bioequivalence and bioavailability studies were conducted. A total of 2 pivotal human pharmacokinetic studies (Study PL-ASA-001 and Study PL-ASA-003) have been submitted in support of this NDA. Study PL-ASA-001 is a randomized, actively controlled, cross-over bioequivalence study and Study PL-ASA-003 is a randomized, actively controlled, cross-over food effect (bioavailability) study.

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).*

*Genuine Bayer® Aspirin, 325 mg tablet is identified by the Sponsor, but it is legally marketed under a tentative final monograph.

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

APPEARS THIS WAY ON ORIGINAL

RELIANCE ON LISTED DRUG(S)

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

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

YES ☐ NO ☒

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

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

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

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 monograph?

YES ☐ NO ☐

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

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

YES ☐ NO ☐

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

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

This application provides for a change in dosage form, from tablet to liquid-filled capsule. The product is a novel liquid-filled capsule containing a lipidic suspension of aspirin that does not conform to the Dissolution Testing specification required in the TFM (53 Fed. Reg. at 46260, Subpart D–Testing Procedures) as defined in the USP monograph for Aspirin Capsules. Moreover, the lecithin excipient (b) (4) used in the drug product (b) (4) the approved amount listed in the FDA inactive ingredients guide (IIG) for an orally administered drug product.

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

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

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

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

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

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

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

YES ☐ NO ☐

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

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

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

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

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

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

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

YES ☐ NO ☐

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

YES ☐ NO ☐

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

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

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

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

YES ☐ NO ☐

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

Listed drug/Patent number(s):

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

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

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

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

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

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

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

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

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

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

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

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

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

Date(s):

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

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

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

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

/s/

JANICE ADAMS
12/26/2012

Labeling Review for Aspirin Capsules

SUBMISSION DATES:	March 12, 2012 May 21, 2012 August 3, 2012
NDA/SUBMISSION TYPE:	203697 (PA)
ACTIVE INGREDIENTS:	Aspirin 325 mg
DOSAGE FORMS:	Capsule, liquid-filled
SPONSOR:	PLx Pharma Inc. 8285 El Rio Street, Suite 130 Houston, Texas 77054 Jason E. Moore Vice President (713) 842-1249
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD

I. BACKGROUND

NDA 203697 is submitted by PLx Pharma for Aspirin (acetylsalicylic acid) capsules, 325 mg for immediate release for use as a pain reliever/fever reducer. The sponsor states that their product conforms to the tentative final monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (IAAA TFM, 53 FR 46204, November 16, 1988) with one exception. The drug product, a liquid-filled capsule containing a lipidic suspension of aspirin, does not conform to the Dissolution Testing specification required in the TFM (53 FR 46260) as defined in the USP monograph for Aspirin Capsules. Also, the lecithin excipient (b) (4) used in the drug product (b) (4) the approved amount listed in the FDA inactive ingredients guide for an orally administered drug product. During the IND stage FDA advised PLx Pharma that PL2200 requires NDA approval.

One labeling issue was included in the 74-day letter sent on May 22, 2012: "Provide detailed annotated font specifications for Drug Facts for all SKUs you intend to market."

Submitted Labeling	Representative of Following SKUs
30-count bottle and carton	N/A
120-count bottle and carton	N/A
7-count blister card	N/A
7-count blister carton	N/A
28-count blister carton	N/A

The initial labeling submission was for the (b) (4) trade name. New labels for the (b) (4) trade name were submitted May 21, 2012 and are reviewed here. Complete annotated font specifications for Drug Facts were submitted on August 3, 2012.

II. REVIEWER'S COMMENTS

A. All SKUs

i. Outer Carton Label Outside Drug Facts

a. Principal Display Panel (PDP)

1. Trade name

The labels submitted on May 21, 2012, which include the trade name (b) (4), are reviewed here. In a letter to the sponsor dated August 17, 2012, DMEPA found the trade name (b) (4) unacceptable. The sponsor should submit revised labels with a new trade name or without a trade name and using the established name for the product.

2. Statement of Identity

The statement of identity does not follow the standard format. According to 21 CFR 201.61(b), the statement of identity "… shall be in terms of the established name of the drug…followed by an accurate statement of the general pharmacological category(ies) …". The trade name and statement of identity should be in the following format:

Trade name
Established name, dosage form, dosage strength
Pharmacological category

Or

Trade name
Established name, dosage strength
Dosage form
Pharmacological category

Also, to comply with 21 CFR 201.61(c), the statement of identity should be in bold type in a size reasonably related to the most prominent printed material on the PDP, that is, the trade name.

3. **NSAID designation**
   According to 21 CFR 201.326(a)(2)(i), the designation "(NSAID)" must appear highlighted or in bold type as part of the statement of identity.
4. **Liquid Filled Capsules**
   The term "capsule" can be used to describe the dosage form in the statement of identity above. However, the phrase "Liquid Filled Capsules" is an FDA recognized dosage form and provides a better description of the type of capsules. We recommend including this in the net quantity of contents, so for example, the net quantity of contents for the 30-count size would be listed as "30 Liquid Filled Capsules".
5. (b) (4)
   (b) (4)
6. **Promotional language on PDP**
   The phrases (b) (4) are considered promotional language that may be misleading by implying a superiority claim (b) (4) and should be removed from the PDP.
   Using the phrase (b) (4) on the PDP is not acceptable because (b) (4) The name (b) (4) is considered promotional. While some consumers may interpret the word (b) (4) to imply an unknown benefit, most consumers would find the term meaningless. The phrase (b) (4) should be removed from the carton label.

ii. **Side Panels**

a. **Statement of Identity**
   The side panels should reflect the changes made to the statement of identity as describe above in II.A.i.a.2. and 3.

b. **Tamper evident statement (30-count and 120-count cartons)**
   The outer carton for the bottle SKUs contains the phrase "Tamper evident: Do not use if imprinted safety seal under cap is missing or broken". According to 21 CFR 211.132(c)(2), if the tamper-evident feature uses an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture), the identifying characteristic should be included in the tamper-evident label statement. If the imprinted safety seal uses an identifying characteristic, the tamper evident statement must be revised to include the identifying characteristic.

iii. Outer Carton Drug Facts Label for all SKUs

a. Active ingredient

The active ingredient listing follows the IAAA TFM monograph (53 FR 46255) and the NSAID requirement and optional highlighting under 21 CFR 201.326(a)(2)(ii). This section of the label is acceptable.

b. Uses

The indications listed on the label under "***Uses***" follow the proposal in the IAAA TFM (53 FR 46355) and are acceptable with the following format changes. A bullet should be inserted before the phrase "for the temporary relief of minor aches…". The bullet should be separated from the heading by at least two square "ems" (i.e. two squares of the size of the letter "M"). (See 21 CFR 201.66(d)(4).) Since "temporarily reduces fever" is a separate indication from "aches and pains", for clarity, we recommend that this be on a separate line for the 7- and 28-count cartons (similar to how it appears in the "***Uses***" section for the 30- and 120-count cartons). Making these changes will help align the bullets, which are not aligned in the submitted label (See 21 CFR 201.66(d)(4).)

c. Warnings

1. Reye's syndrome

This warning is missing the word "should" in the statement, "Children and teenagers who have or are recovering from chicken pox or flu-like symptoms *should* not use this product." (See 21 CFR 201.314(h)(1).)

2. Allergy Alert

This standard warning contains the same content as the allergy alert warning in the IAAA PR (68 FR 33429) and is acceptable. In addition, below the allergy alert warning, the label carries the statement "This product contains soy." The product does contain soy lecithin which is listed in the inactive ingredients. There is no required language relating to soy in drug products. As soy can cause an allergic reaction in some consumers, this reviewer has no objections to the soy statement on the label to better inform consumers.

3. Stomach bleeding warning

This warning is missing the word "stomach" in the statement "This product contains an NSAID, which may cause severe *stomach* bleeding." (See 21 CFR 201.326(a)(2)(iii)(A).)

4. Do not use

The statement advising consumers not to use the product if the user has had an allergic reaction to aspirin or any other pain reliever/fever reducer follows the requirement in the IAAA PR (68 FR 33429) and is acceptable.

5. Ask a doctor before use if

This section follows 21 CFR 201.326(a)(2)(iii)(B) with the asthma warning (53 FR 46256) and is acceptable with the following revision. The word "a" should be removed from the statement "you have <u>a</u> high blood pressure, heart disease, liver cirrhosis, or kidney disease" for readability and to agree with the regulation.

6. Ask a doctor or pharmacist before use

The first two bullets can be deleted. These are:

[redacted] (b) (4)

These bullets are covered by the stomach bleeding warning and the statement under "**Ask a doctor before use**" if the stomach bleeding warning applies to you. (See 81 FR 19400 and 21 CFR 201.326(a)(2)(iii)(A) and (B).)

7. **Stop use and ask a doctor if**

This section includes the warnings related to allergy in the IAAA PR (68 FR 33429), stomach bleeding in 21 CFR 201.326(a)(2)(iii)(C), and ototoxicity warning in IAAA TFM (53 FR 46256) and is acceptable with the following revisions. Two statements should be revised so that they are consistent with the NSAID template (67 FR 54150) which presents Drug Facts format for the IAAA warnings (53 FR 46256):

[redacted] (b) (4) should be changed to
"[bullet] fever get worse or lasts for more than 3 days"

[redacted] (b) (4) should be changed to
"[bullet] redness or swelling is present in the painful area"

The statement [redacted] (b) (4) (b) (4) . As a toll free number is included under "***Questions or comments***", these statements can be removed from the label.

8. **Pregnancy/breast feeding warning**

This warning agrees with 21 CFR 201.63(e) and is acceptable.

9. **Keep out of reach of children (30- and 120-count cartons)**

This warning is required under 21 CFR 201.314(a) and 21 CFR 330.1(g) but is missing from the 30- and 120-count carton Drug Facts labels.

d. Directions

The directions allow for one or two capsules every 4 hours or three capsules every 6 hours, not to exceed 12 capsules in 24 hours. This agrees with the recommendations in the IAAA TFM (53 FR 46257). The phrase "while symptoms persist" should be added after "…every 6 hours". (See 53 FR 46257 and NSAID template [67 FR 54150].)

e. Other information

1. **Storage conditions**

The "°" (degree) symbol is missing from the storage conditions. These statements should be corrected to read:

[bullet] store at 15 - 30°C (59 - 86°F)
[bullet] avoid excessive heat above 40°C (80°F)

2. **Tamper evident statement (7- and 28-count cartons)**

According to 21 CFR 211.132(c)(1)(i), each retail package is required to identify all tamper evident features. As the blister card is a tamper evident feature, a statement to the effect that the consumer should not use the product if the blister is open or torn should be included here.

3. **Bullet alignment (7- and 28-count cartons)**
   As these cartons do not meet the requirements for the modified labeling format 21 CFR 201.66 (d)(10), a bulleted statement placed on the same line as another bulleted statement is not allowed to wrap to the next line (see 21 CFR 201.66(d)(4). The statement "[bullet] do not use if blue band…" should be moved to the next line and vertically aligned with other bulleted statements.

f. Inactive ingredients
The wording (b) (4) should be removed and all inactive ingredients listed alphabetically (See 21 CFR 201.66(c)(8).)

g. Questions or comments
This section follows 21 CFR 201.66(c)(9) and is acceptable.

h. Specifications
The following format changes not described previously should be made in the labels to comply with the font specifications listed in 21 CFR 201.66:

1. Only the first letter should be capitalized in the headings, "***Other information***" and "***Questions or comments***" (See 21 CFR 201.66(d)(1).)
2. **(7- and 28-count cartons)** The "**Do not use**" subheading is 7-point type size and should be made consistent with all other subheadings that are 6-point type size. FDA strongly recommends uniformity of Drug Facts presentation as shown in appendix A to Part 201. (See 21 CFR 201.66(d).)
3. **(7- and 28-count cartons)** A hairline should follow the statement "[bullet] you have asthma" under the subheading "**Ask a doctor before use**" and precede the heading "**Ask a doctor or pharmacist before use if you are**". (See 21 CFR 201.66(d)(8).)

iv. Immediate Container labels

a. 30- and 120-count bottle labels

1. PDP
The PDP on the bottles should be revised to agree with the recommendations made for the carton PDP as described above under II.A.i.a.

2. Drug Facts
Drug Facts recommendations for the carton should be made to the bottle labels as described above under II.A.iii.

3. Annotated specifications were submitted for the four carton labels. Since the 30- and 120-count bottles use Drug Facts labeling, these labels should comply with the requirements of 21 CFR 201.66 and the annotated specifications for these labels should be submitted.

b. 7-count blister card

1. It is not necessary for information such as NDC number, storage conditions and tamper statement to be on the blister. This added information tends clutter the blister and distract from more important information. Minimum requirements for the immediate container are listed under 21 CFR 201.10(h)(2)(i).
2. **NSAID identification**
   "(NSAID)" must appear as part of the established name according to 21 CFR 201.326(a)(2)(i)(B).

3. **Stomach bleeding warning**
   The stomach bleeding warning must be added to the blister card as required by 21 CFR 201.326(a)(2)(iii)(A).
4. **Reye's syndrome warning**
   The Reye's syndrome warning must be added to the blister card as required by 21 CFR 201.314(h)(1) and (2).

III. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the labeling deficiencies listed below. These deficiencies are based on our preliminary labeling review. Further labeling recommendations may be forthcoming.

Outer Carton Principal Display Panel (PDP) on all SKUs

1. The statement of identity does not follow the standard format. According to 21 CFR 201.61(b), the statement of identity "… shall be in terms of the established name of the drug…followed by an accurate statement of the general pharmacological category(ies) …". The trade name and statement of identity should be in the following format:

   Trade name
   Established name, dosage form, dosage strength
   Pharmacological category

   Or

   Trade name
   Established name, dosage strength
   Dosage form
   Pharmacological category

2. To comply with 21 CFR 201.61(c), the statement of identity should be in bold type in a size reasonably related to the most prominent printed material on the PDP, that is, the trade name.

3. According to 21 CFR 201.326(a)(2)(i), the designation "(NSAID)" must appear highlighted or in bold type as part of the statement of identity.

4. The term "capsule" can be used to describe the dosage form in the statement of identity. However, the phrase "Liquid Filled Capsules" is an FDA recognized dosage form and provides a better description of the type of capsules and should be included in the net quantity of contents. For example, the net quantity of contents for the 30-count size would be listed as "30 Liquid Filled Capsules".

5. [redacted].

6. The phrases [redacted] are considered promotional language and may be misleading by implying a superiority claim [redacted], and should be removed from the PDP.

7. Using the phrase [redacted] on the PDP is not acceptable because [redacted]. The name [redacted] is considered promotional. While some consumers may interpret the word [redacted] to imply an unknown benefit, most consumers would find the term meaningless. The phrase [redacted] should be removed from the carton label.

Outer Carton Side Panels on all SKUs

1. The side panels should reflect the changes made to the statement of identity as described above.

Outer Carton Side Panels (30-count and 120-count cartons)

1. The outer carton for the bottle SKUs contains the phrase "Tamper evident: Do not use if imprinted safety seal under cap is missing or broken". According to 21 CFR 211.132(c)(2), if the tamper-evident feature uses an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture), the identifying characteristic should be included in the tamper-evident label statement. If the imprinted safety seal uses an identifying characteristic, the tamper evident statement should specify the identifying characteristic.

Outer Carton Drug Facts Label on all SKUs

1. **Uses –** Under the ***Uses*** heading, a bullet should be inserted before the phrase "for the temporary relief of minor aches…". The bullet should be separated from the heading by at least two square "ems" (i.e. two squares of the size of the letter "M"). (See 21 CFR 201.66(d)(4).) Making these changes will help align the bullets, which are not aligned in the submitted labels (See 21 CFR 201.66(d)(4).)
2. **Warnings**
   a. **Reye's syndrome**
   This warning is missing the word "should" in the statement, "Children and teenagers who have or are recovering from chicken pox or flu-like symptoms *should* not use this product." (See 21 CFR 201.314(h)(1).)

b. Stomach bleeding warning

This warning is missing the word "stomach" in the statement "This product contains an NSAID, which may cause severe *stomach* bleeding." (See 21 CFR 201.326(a)(2)(iii)(A).)

c. Ask a doctor before use if

The word "a" should be removed from the bulleted statement "[bullet] you have *a* high blood pressure, heart disease, liver cirrhosis, or kidney disease" for readability and to agree with 21 CFR 201.326(a)(2)(iii)(B).

d. Ask a doctor or pharmacist before use

The first two bulleted statements under this heading should be deleted. These are: (b) (4)

These statements are covered by the stomach bleeding warning and the statement under "**Ask a doctor before use**" if the stomach bleeding warning applies to you. (See 21 CFR 201.326(a)(2)(iii)(A) and (B).)

e. Stop use and ask a doctor if

Two statements under this heading should be revised so that they are consistent with the NSAID template (67 FR 54150) which presents Drug Facts format of the IAAA warnings (53 FR 46256):

(b) (4) should be changed to
"[bullet] fever get worse or lasts for more than 3 days"
(b) (4) should be changed to
"[bullet] redness or swelling is present in the painful area"

The following statement is not required: (b) (4) (b) (4) . As a toll free number is included under the "***Questions or comments***" heading, these statements can be removed from the label.

3. Directions

The phrase "while symptoms persist" should be added after "…every 6 hours" so that it reads "[bullet] take 1 or 2 capsules every 4 hours or 3 capsules every 6 hours while symptoms persist". (See 53 FR 46257 and NSAID template [67 FR 54150].)

4. Other information

Storage conditions

The "°" (degree) symbol is missing from the storage conditions. These statements should be corrected to read:

[bullet] store at 15 - 30°C (59 - 86°F)
[bullet] avoid excessive heat above 40°C (80°F)

5. Inactive ingredients

The wording (b) (4) should be removed and all inactive ingredients listed alphabetically (See 21 CFR 201.66(c)(8).)

6. Drug Facts Specifications

Only the first letter should be capitalized in the headings, "***Other information***" and "***Questions or comments***" (see 21 CFR 201.66(d)(1)).

Outer Carton Drug Facts Label (30- and 120-count cartons)

1. **Keep out of reach of children**
   This warning is required under 21 CFR 201.314(a) and 21 CFR 330.1(g) but is missing from the 30- and 120-count carton Drug Facts labels.

Outer Carton Drug Facts Label (7- and 28-count cartons)

1. **Uses**
   Since "temporarily reduces fever" is a separate indication from "aches and pains", for clarity, we recommend that this be on a separate line for the 7- and 28-count cartons (similar to how it appears in the "***Uses***" section on the 30- and 120-count cartons).
2. **Other information**
   Tamper evident statement
   According to 21 CFR 211.132(c)(1)(i), each retail package is required to identify all tamper evident features. As the blister card is a tamper evident feature, a statement to the effect that the consumer should not use the product if the blister is open or torn should be included here.
3. **Drug Facts Specifications**
   a. The "**Do not use**" subheading is 7-point type size and should be made consistent with all other subheadings that are 6-point type size. FDA strongly recommends uniformity of Drug Facts presentation as shown in appendix A to Part 201. (See 21 CFR 201.66(d).)
   b. A hairline should follow the statement "[bullet] you have asthma" under the subheading "**Ask a doctor before use**" and precede the heading "**Ask a doctor or pharmacist before use if you are**". (See 21 CFR 201.66(d)(8).)
   c. Other information - As these cartons do not meet the requirements for the modified labeling format under 21 CFR 201.66 (d)(10), a bulleted statement placed on the same line as another bulleted statement is not allowed to wrap to the next line (see 21 CFR 201.66(d)(4). Under the "***Other information***" heading, the statement "[bullet] do not use if blue band…" should be moved to the next line and vertically aligned with other bulleted statements.

Immediate Container labels (30-count and 120-count bottle labels)

1. **PDP**
   The PDP on the bottles should be revised to agree with the recommendations made for the carton PDP as described above.
2. **Drug Facts**
   Drug Facts recommendations for the carton should be made to the bottle labels as described above.
3. **Annotated specifications** were submitted for the four carton labels. Since the 30- and 120-count bottles use Drug Facts labeling, these labels should comply with the requirements of 21 CFR 201.66 and the annotated specifications for these labels should be submitted.

Immediate Container labels (7-count blister card)

1. It is not necessary for information such as [redacted] (b) (4) to be on the blister. This added information tends clutter the blister and distract from more important information. Minimum requirements for the immediate container are listed under 21 CFR 201.10(h)(2)(i).
2. **NSAID identification**
   "(NSAID)" must appear as part of the established name according to 21 CFR 201.326(a)(2)(i)(B).
3. **Stomach bleeding warning**
   The stomach bleeding warning must be added to the blister card as required by 21 CFR 201.326(a)(2)(iii)(A).
4. **Reye's syndrome warning**
   The Reye's syndrome warning must be added to the blister card as required by 21 CFR 201.314(h)(1) and (2).

Issue a communication to the sponsor that includes these deficiencies in order to initiate labeling negotiations.

IV. SUBMITTED LABELING

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

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

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

/s/

ELAINE E ABRAHAM
12/10/2012

STEVEN A ADAH
12/10/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products, HFD-170

MEMORANDUM

DATE: December 6, 2012

FROM: Christina Fang, M.D., M.P.H.

THROUGH: Sharon Hertz, M.D., Deputy Division Director, DAAAP

SUBJECT: Literature review of analgesic and antipyretic studies of aspirin submitted in NDA 203697

TO: Janice Adams-King, Division of Nonprescription Clinical Evaluation, ODE IV

Background
The Division of Nonprescription Clinical Evaluation (DNCE) has consulted the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for a review of literature reports of studies in which aspirin was included as one of the treatment arms. These literature reports were submitted by the Applicant of NDA 203697. DNCE has requested that the literature review be focused on the time period staring 1988, the year of publication of the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use.

Literature review
This literature review is limited to the publications selected and submitted by the Applicant of NDA 203697.

The studies to be included in the review were selected by the reviewer based on the following criteria: randomized, double-blind, placebo-controlled study design and published later than 1988, except an additional fever study published in 1979 and three dysmenorrhea studies published in the early eighties were included because only one fever study and no dysmenorrhea studies were published in the specified time frame.

Key information about the studies are summarized in the tables below in terms of the year and the author of publication, the country of the study site, trial design, treatment arms, sample size per treatment arm, estimated effect size of treatment difference between aspirin and placebo, and comments about the findings. The common features shared between all the analgesic studies, except dysmenorrhea studies, are single-dose, availability of pain intensity difference (PID) curves or time-specific PID data, and no data collection for onset by stopwatch or duration by rescue/remedication. Only dysmenorrhea studies had multiple-dose evaluations reported as a single endpoint of average pain instead of time-specific measurements. Because of the variability in study endpoints (no endpoints in some of the studies) and sample sizes (ranging from 20 to 500 subjects per study group) in these studies, the primary focus of this review is on the estimated effect size of treatment difference between aspirin and placebo based on PID data or PID curves.

Summary tables

Fever

Citation Study site	Design (R/DB/PC)	Dosage Treatment arm	n	Estimated effect size of treatment difference between ASA & placebo	Reviewer's comments
Bachert et al. 2005 Ukraine and Russia	Randomized (R) double-blind (DB) placebo-controlled (PC) parallel	Single dose ***ASA 500 mg*** ***ASA 1000 mg*** APAP 500 mg APAP 1000 mg Placebo	 78 78 79 79 78	Differences in temperature reduction $>0.5^0$C from 1 to 6 hours for both ASA 500 & 1000 mg doses (refer to Figure 1)	Effect size suggests clinically meaningful treatment difference for up to 6 hours Dose response suggested by separation between two ASA temperature curves
Cashman et al. 1979 USA	R/DB/PC parallel pediatric (age 3-12 years	Single dose ***ASA 15 mg/kg*** Nap 2.5 mg/kg Nap 7.5 mg/kg Placebo	 25 27 27 30	Differences in temperature reduction $\geq 1.0^0$F from 1 to 5 hours (refer to Figure 2)	Effect size suggests clinically meaningful treatment difference for up to 5 hours

Headache

Citation Study site	Design (R/DB/PC)	Dosage Treatment arm	n	Estimated effect size of treatment difference between ASA & placebo	Reviewer's comments
MacGregor et al. 2002 UK	R/DB/PC crossover migraine	Single dose ***ASA 900 mg*** Placebo	101	Difference in PID =0.4 (4-pt scale) at Hr 0.75 and 1 and >0.5 from Hr 2-6 (refer to Table 1) PR not measured	Effect size suggests clinically meaningful treatment difference for up to 6 hours
Martinez-Martin et al. 2001 Spain	R/DB/PC parallel tension type headache	Single dose ***ASA 1 g*** Metamizol 0.5 g Metamizol 1g Placebo	 91 83 95 91	Difference in PID >10 mm (on 100 mm VAS scale) at Hr 4; Difference in PR >0.5 (on 5-pt scale) from Hr 3 to 4 (refer to Table 2)	Small treatment difference due to high placebo responses
Pfaffen-rath et al. 2009 Germany	R/DB/PC parallel	Single dose ASA500/PARA200/CAF50 ASA500/PARA200 ***ASA 1000 mg*** PARA 1000 mg CAF 50 mg Placebo	 482 498 252 251 132 128	Difference in PID >10 mm (on 100 mm VAS scale) Hr 1-4 (refer to Figure 3); PR not measured	Effect size suggests clinically meaningful treatment difference for up to 4 hours
Steiner et al. 2003 UK	R/DB/PC parallel	Single dose ***ASA 500 mg*** ***ASA 1000 mg*** PARA 500 mg PARA 1000 mg Placebo	 111 103 105 111 112	Difference in PID >10 mm (on 100 mm VAS scale) Hr 1-4 for both ASA 500 & 1000 mg (refer to Figure 4); PR curves not available	Effect size suggests clinically meaningful treatment difference in PID for up to 4 hours. Dose response not supported by two ASA pain curves

Sore throat

Citation Study site	Design (R/DB/PC)	Dosage Treatment arm	n	Estimated effect size of treatment difference between ASA & placebo	Reviewer's comments
Eccles et al. 2003 UK	R/DB/PC parallel	Single dose ***ASA 800 mg*** Placebo	 139 133	Difference in PID ≥0.75 (on 11-pt numerical scale) during Hr 1-3 (refer to Figure 5); PR curves not available	Effect size suggests clinically meaningful treatment difference for up to 3 hours
Schachtel et al. 1991 USA	R/DB/PC parallel	Single dose ASA 800mg/Caffeine 64mg ***ASA 800 mg*** Placebo	 70 68 69	Difference in PID ≥20 (on 200 mm VAS scale) from Hr 0.5 to 2 (refer to Figure 6); Difference in PR >1.0 (on 5-pt scale) from Hr 0.5 to 2	Effect size suggests clinically meaningful treatment difference in the 2-hour evaluation period

Dysmenorrhea

Citation Study site	Design (R/DB/PC)	Dosage Treatment arm	n	Estimated effect size of treatment difference between ASA & placebo	Reviewer's comments
DeLia et al. 1982 USA	R/DB/PC crossover	Multiple dose ***ASA 650 mg*** Flurbiprofen 50 mg Placebo q6h for >1 day	59	Difference in mean PR= 0.42 (on a 5-point scale); No time-specific measurements of PI or PR	Borderline effect size
Klein et al. 1981 USA	R/DB/PC crossover adolescent	Multiple dose ***ASA 600 mg*** Placebo 4x/day for 4 periods	47	Difference in pain=1.4 (on 6-point scale by Menstrual Distress Questionnaire); No time-specific measurements of PI or PR	Effect size suggests clinically meaningful treatment difference
Pender-grass et al. 1985 USA	All on placebo in 1st 2 periods followed by R/DB/PC assignment into 3 arms in periods 3 and 4	Multiple dose ***ASA 650 mg*** APAP 650 mg Placebo Q4h for 4 doses	90	Difference in average pain score <0.5 (on 4-point scale); No time-specific measurements of PI or PR	Unusual study design and small treatment difference

Toothache (post-operative dental pain)

Citation Study site	Design (R/DB/PC)	Dosage Treatment arm	N	Estimated effect size of treatment difference between ASA &placebo	Reviewer's comments
Cooper et al. 1992 USA	R/DB/PC parallel	Single dose ***ASA 650 mg*** Oxaprozin 1200 mg Oxaprozin 600 mg Placebo	 28 22 28 26	Difference in PID <0.5 (on 4-pt scale) during Hr 1-5 and reaching 0.7 at Hr 2; Difference in PR >0.5 (on 6-pt scale) during Hr 1-5	Effect size suggests clinically meaningful treatment difference in PR and smaller difference in PID for up to 5 hours
Mehlisch et al. 1990 USA	R/DB/PC parallel	Single dose ***ASA 650 mg*** FS 205-397 250 mg FS 205-397 500 mg Placebo	 40 40 40 41	Difference in PID ≥0.5 (on 4-pt scale) during Hr 1-4; Difference in PR >0.5 (on 5-pt scale) during Hr 1-4	Effect size suggests clinically meaningful treatment difference for up to 4 hours

Discussion

Due to the possibility of various types of limitations found in literature reports such as uncertainty about data quality, study conduct, and data analysis, and due to the lack of detailed information and the unavailability of original data, results reported in the literature are generally not considered adequate support of efficacy in the absence of study reports containing the actual data. Nevertheless, the findings from the studies cited support the finding that aspirin works for treating aches and pains and/or fever in an OTC setting, based on the estimated effect size of treatment differences from pairwise comparisons between various aspirin doses and placebo, using time-specific PID measurements in multiple studies of fever, headache, sore throat, primary dysmenorrhea, and dental pain.

Conclusion

The findings in the cited literature support a finding of efficacy for the use of aspirin for OTC indications of temporary relief of minor ache and pains and temporary reductions of fever as stated in the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use.

Appendix

Figure 1 Bachert et al., 2005

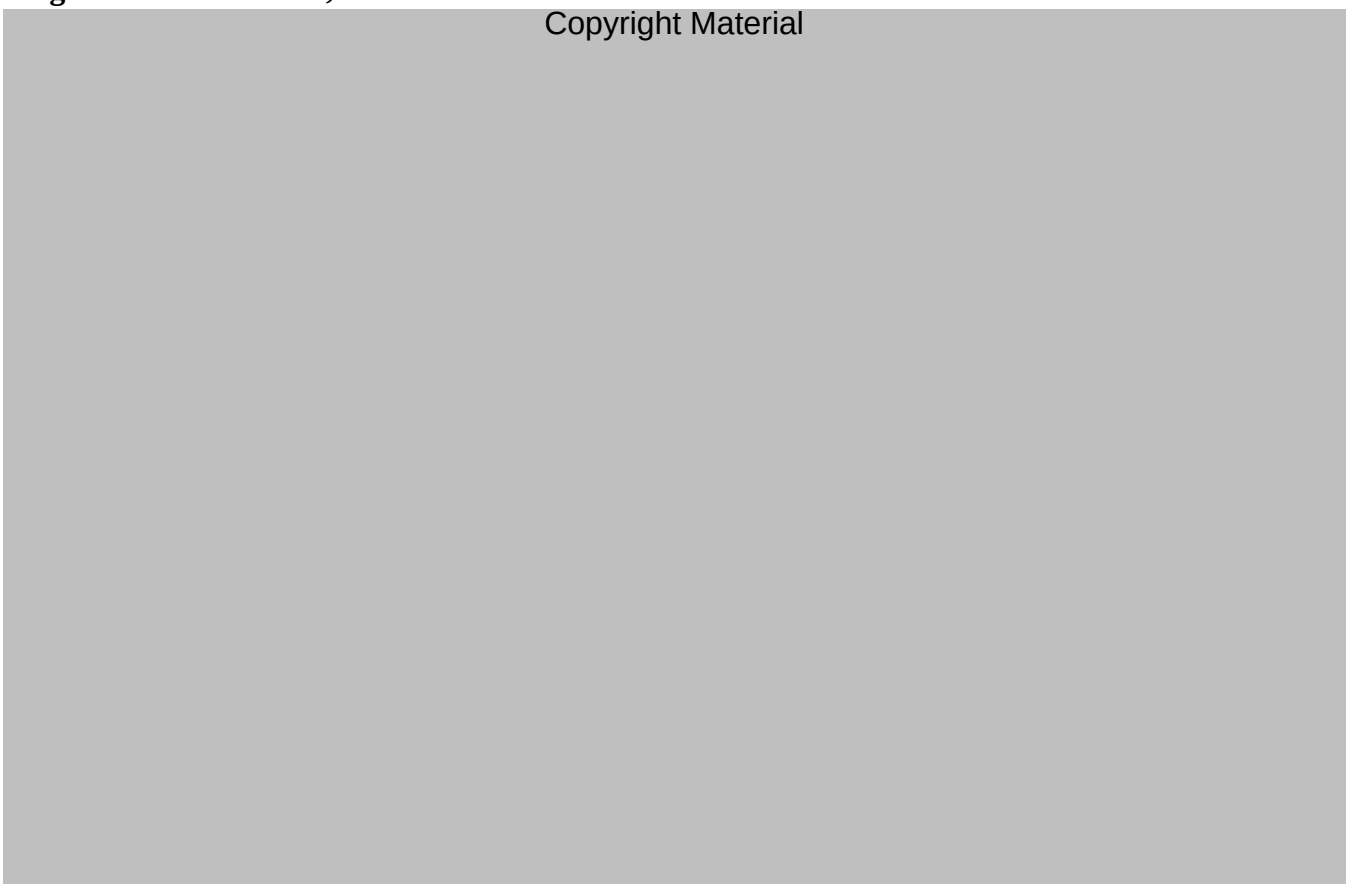

Figure 2 Cashman et al., 1979

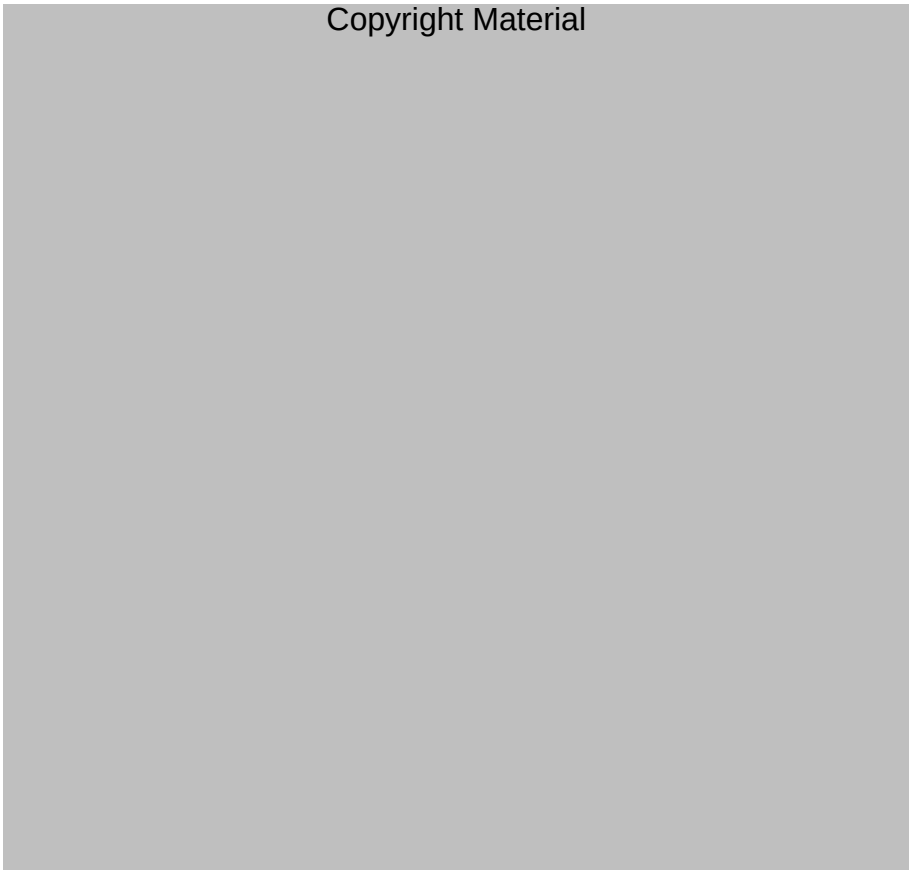

Table 1 MacGregor et al., 2002

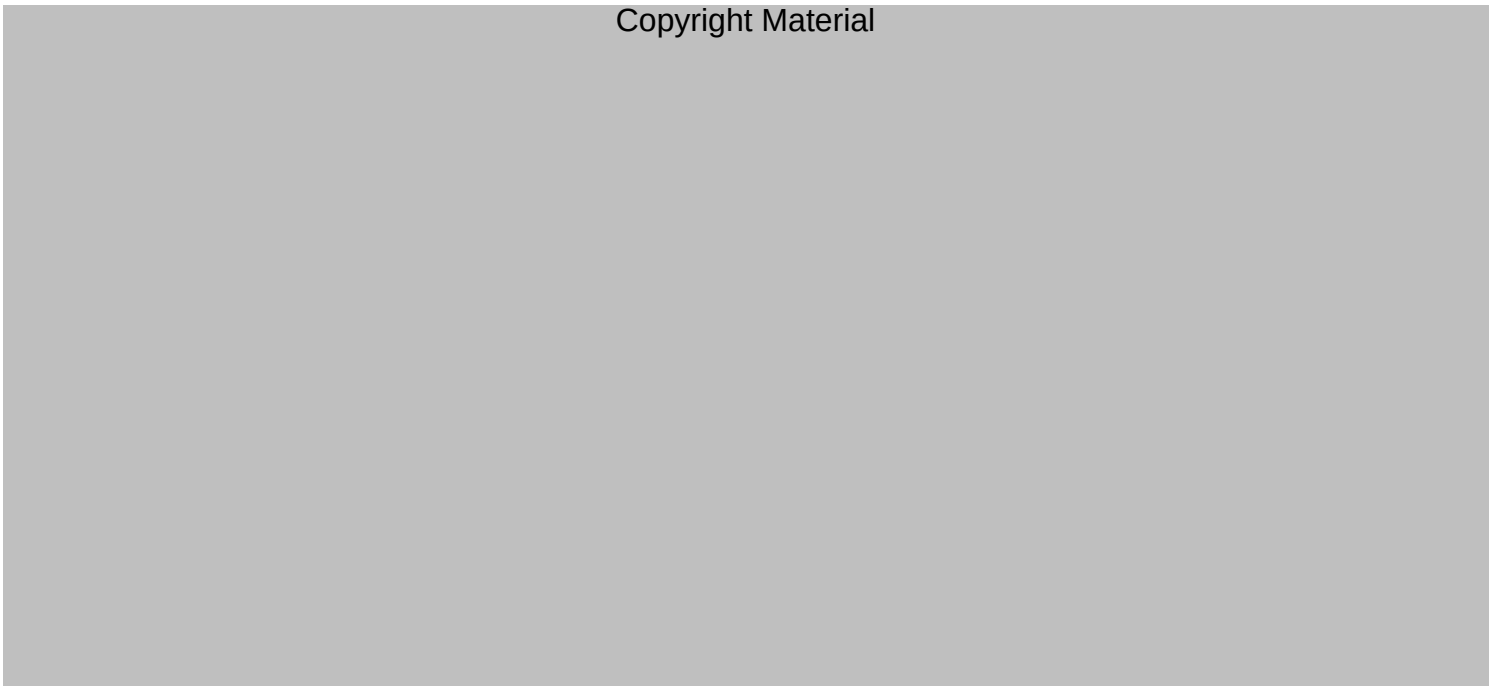

Table 2 Martinez-Martin et al., 2001

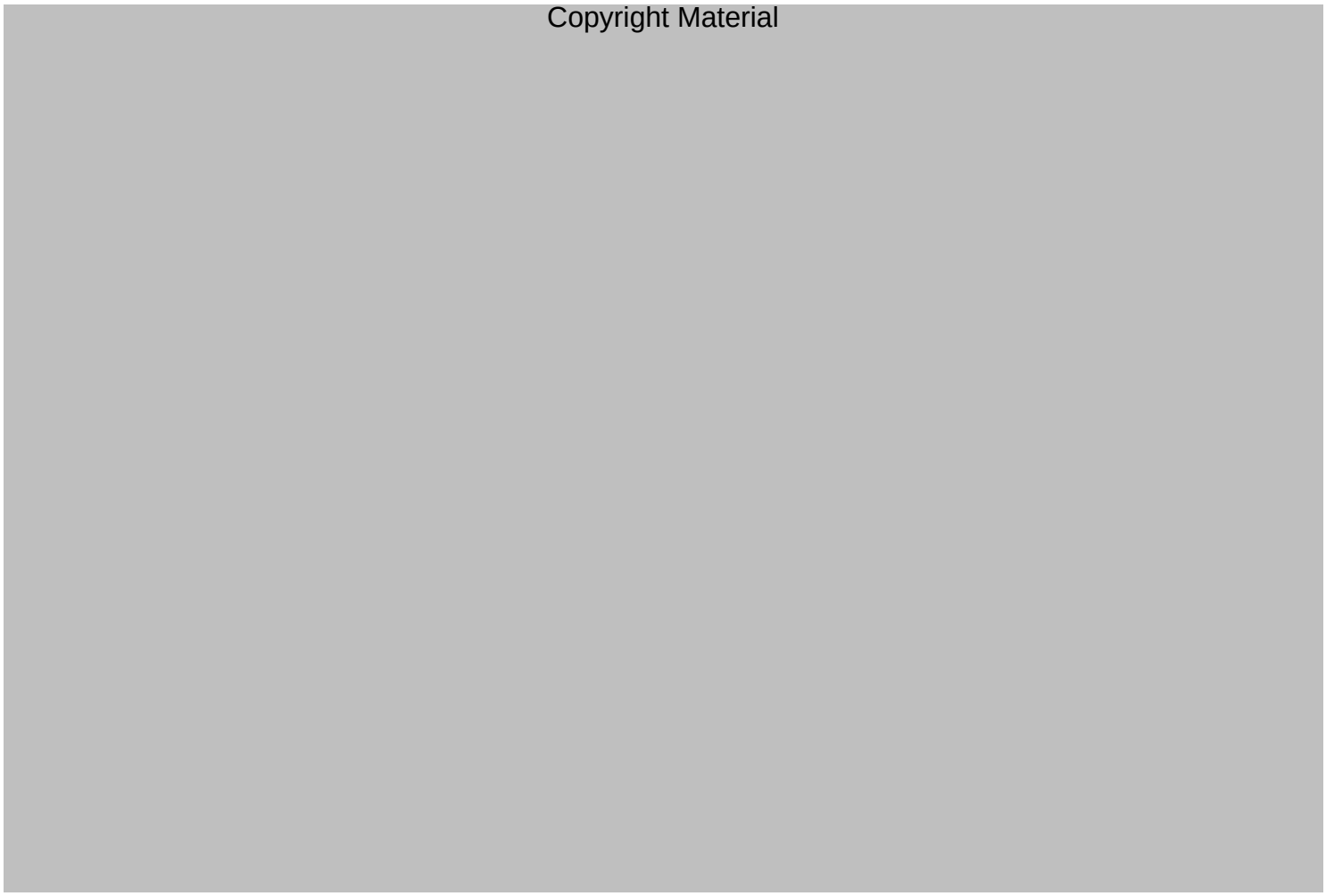

Figure 3 Pfaffen-rath et al., 2009

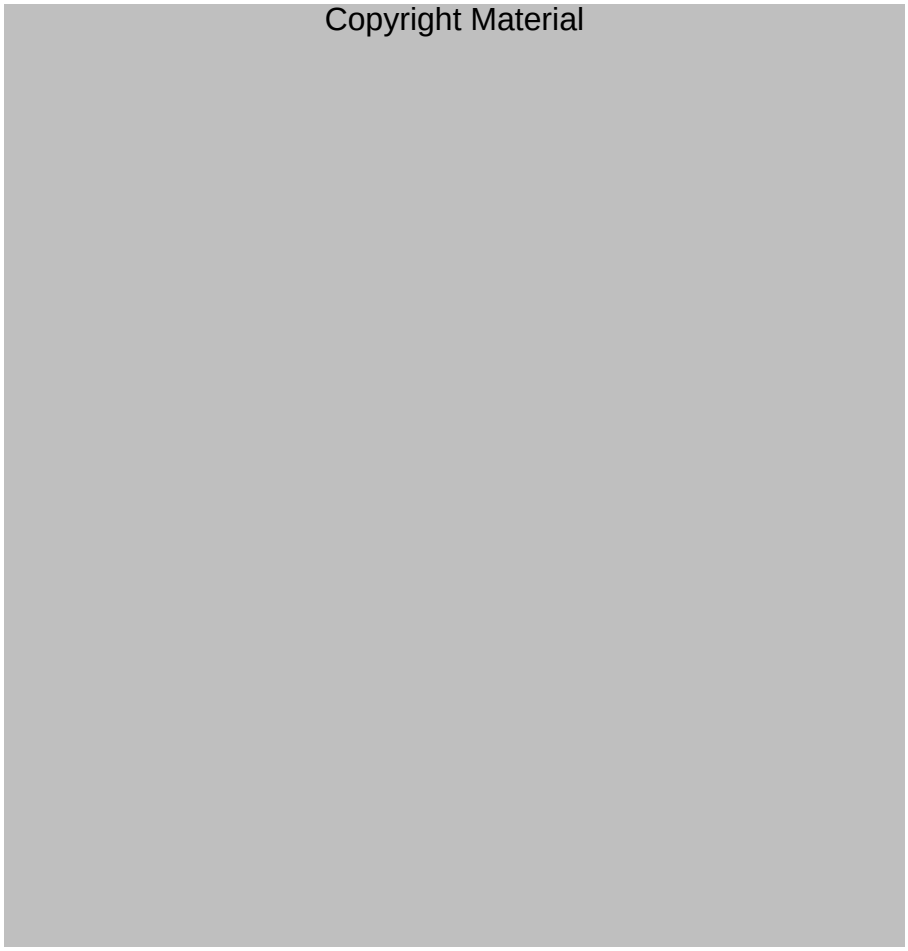

Fig 2.—Time course of the mean pain intensity difference to baseline in the randomized treatment phase when the patients took the randomly allocated study medication for the treatment of their headache attack (full analysis set).ASA = acetylsalicylic acid; CAF = caffeine, PAR = paracetamol.

Figure 4 Steiner et al., 2003

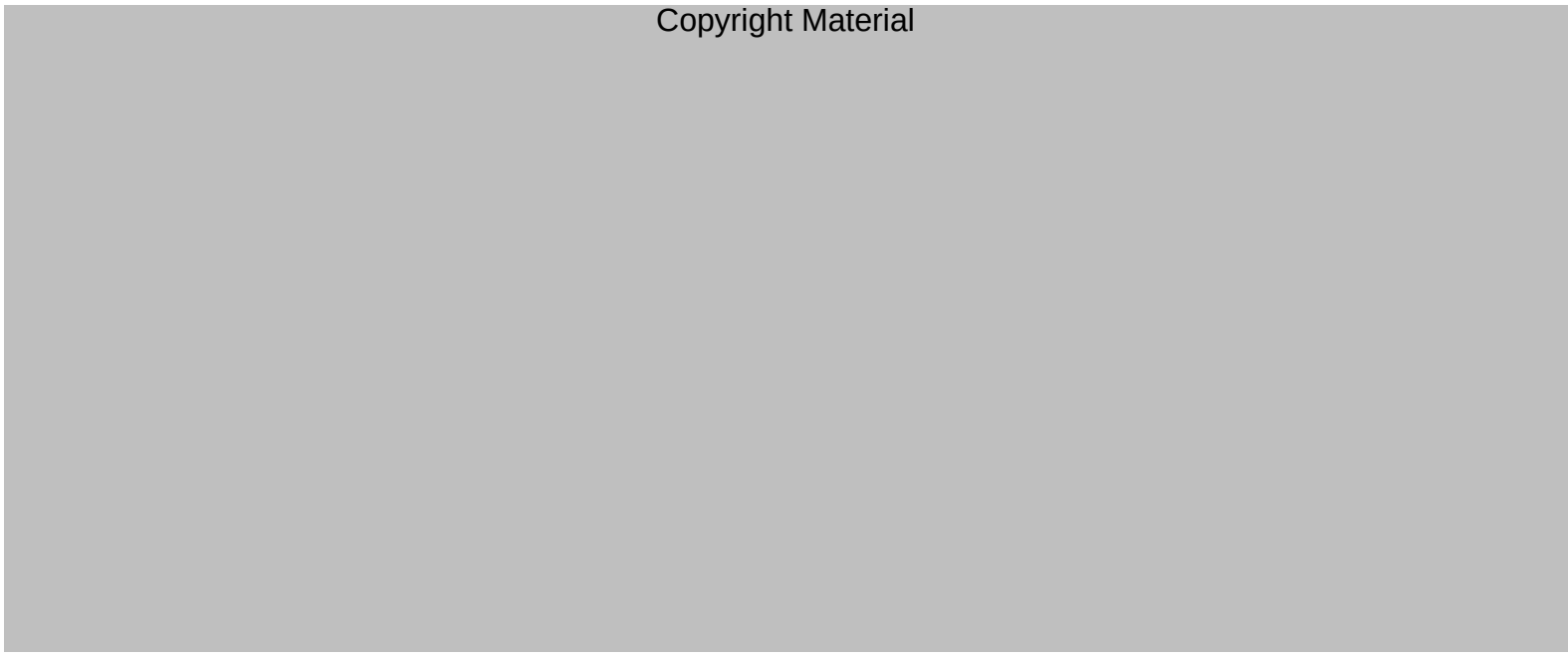

Figure 5 Eccles et al., 2003

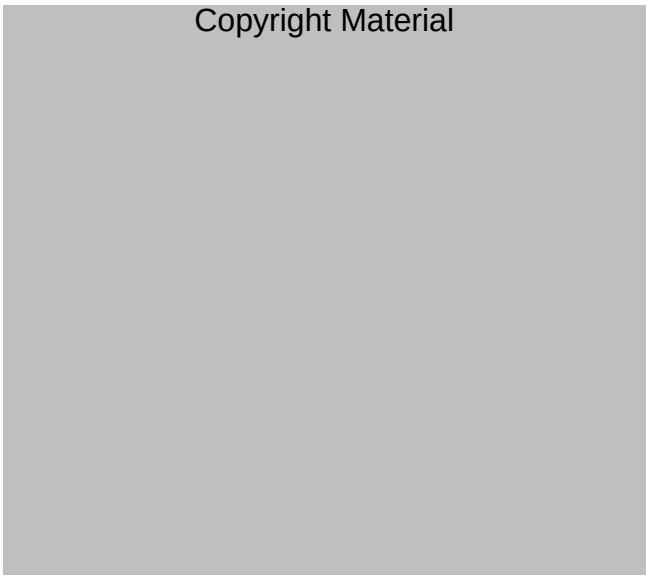

Figure 2 Mean course of PID for sore throat pain with standard deviations. Baseline score minus score at each time point yields positive values for decrease in pain and improvement. N = 139 for ASA, closed symbols; N = 133 for placebo, open symbols.

Figure 6 Schachtel et al., 1991

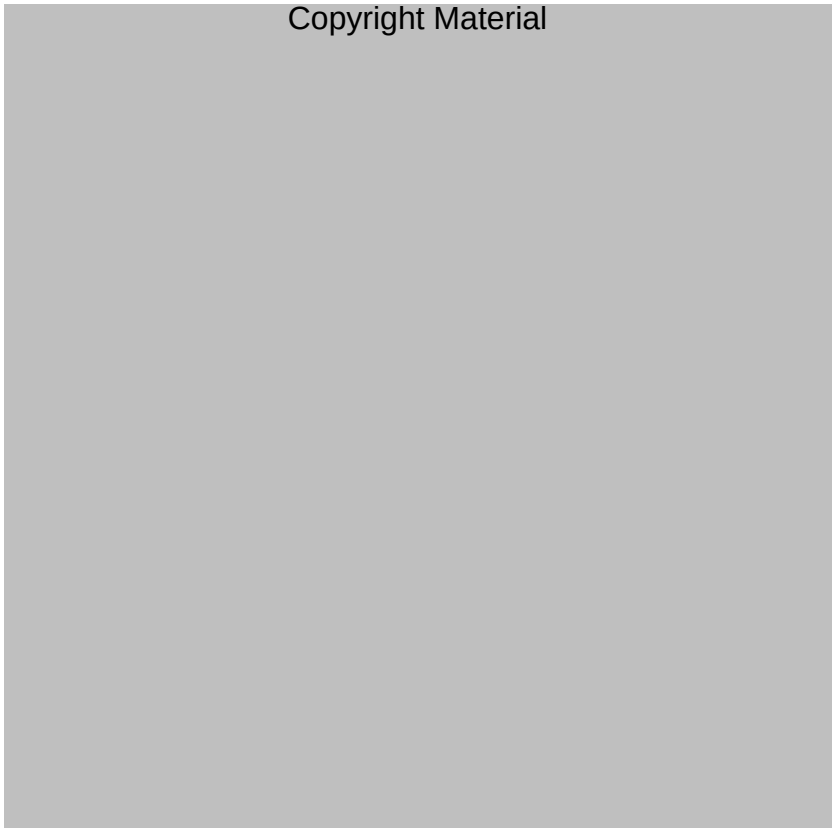

Fig 2.—Change in pain difference from baseline (mean ± SE) using a 200-mm visual analog scale to rate sore throat pain compared with the last time. Aspirin with caffeine and aspirin are significantly different from placebo at 30 to 120 minutes (P<.01). Aspirin with caffeine is significantly different from aspirin at 30 to 120 minutes (P<.05 to P<.01).

Figure 7 Cooper et al., 1992

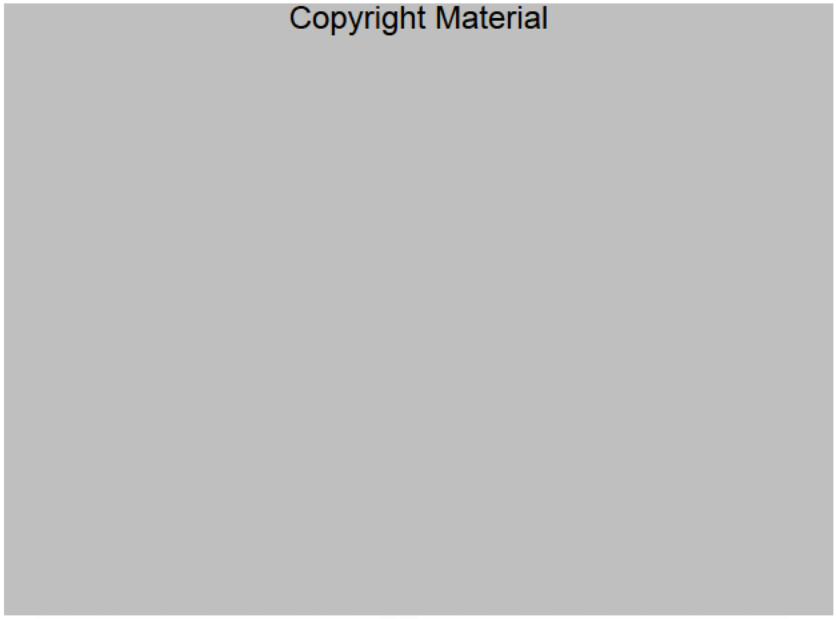

Figure 1 Mean pain intensity difference (PID) scores at each evaluation time point after medication with oxaprozin (0) 600 mg or 1200 mg, aspirin (A) 650 mg, or placebo (P).

Figure 8 Mehlisch et al., 1990

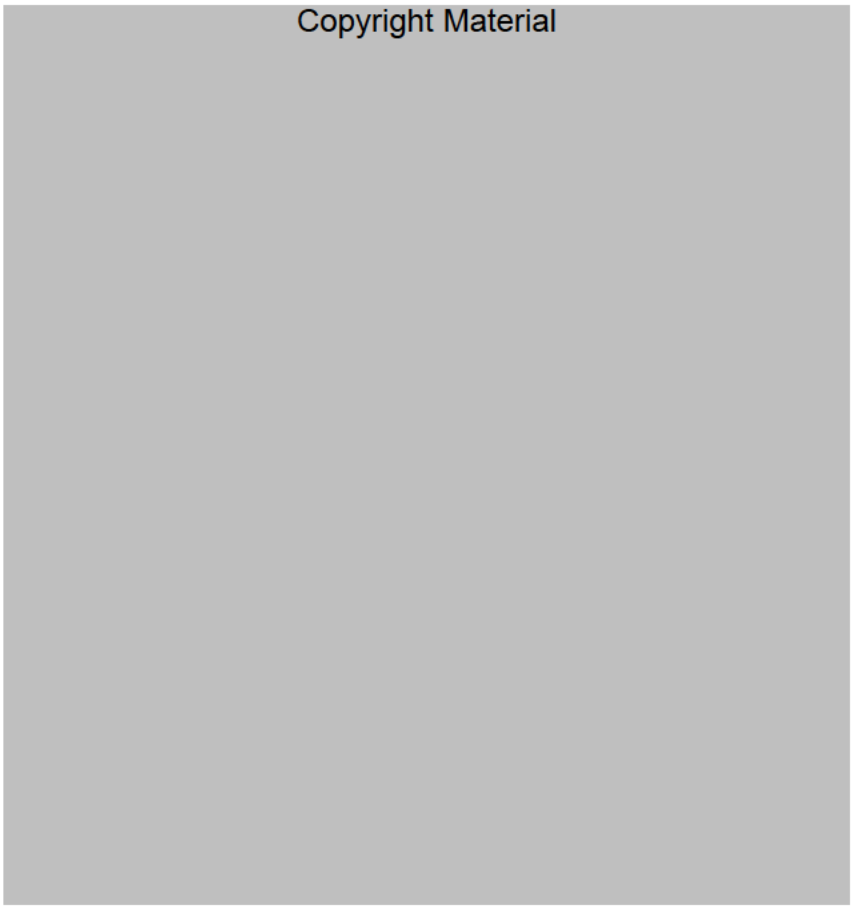

Figure 1 Posttreatment difference in pain intensity at 0.5 hours and hourly thereafter for up to 6 hours (rated on a scale of 1 = none to 4= severe). Higher mean values indicate greater improvement.

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/s/

CHRISTINA L FANG
12/10/2012

SHARON H HERTZ
12/11/2012
I concur.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: November 29, 2012

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products, ODE I

Subject: Antiplatelet effect of PL2200 aspirin, NDA 203-697

Through: Norman Stockbridge, M.D., Ph.D.
Division Director

To: Janice Adams-King
Division of Nonprescription Clinical Evaluation, ODE IV

This memo is our response to your consult dated August 7, 2012 regarding whether PL2200 aspirin is equivalent to approved aspirin in terms of its pharmacodynamic profile when used for its antiplatelet effect. You ask us to review and discuss the data on serum thromboxane, urinary 11-dehyro-TxB2, and *ex vivo* platelet aggregation analyses in terms of appropriateness of methods and equivalence of antiplatelet effect. We summarize the background and data and justify our conclusions below. We conclude that the antiplatelet effects of PL2200 appear equivalent to reference aspirin at the 325 mg dosage. In addition, pharmacokinetic equivalence is nearly achieved. (b) (4)

Background

(b) (4)

(b) (4)

(b) (4)

(b) (4)

NDA studies
The sponsor submitted the results of the three studies shown in Table 1.

Table 1: NDA studies

Study	Type	Doses	Comparator	N
PL-ASA-001	Single dose PK & PD randomized, open-label cross-over study	325, 650	Bayer ASA	32
PL-ASA-002	Randomized, single-blind, 7-day multiple dose, GI endoscopy safety study	325	Walgreens ASA	204
PL-ASA-003	Randomized, open-label, single dose, crossover, food effect PK study	650	(fed vs. fasting)	20

GI = gastrointestinal; PD = pharmacodynamics; PK = pharmacokinetics; ASA = aspirin

Study 002 was a GI endoscopy study that did not provide any data relevant to antiplatelet effect, i.e., it did not include any PK or PD blood sampling. Studies 001 and 003 are typical clinical pharmacology PK/PD studies. Please see the clinical pharmacology reviews for the details of their designs and methodologies.

Appropriateness of Methods and Equivalence of Antiplatelet Effect
The Office of Clinical Pharmacology (OCP) consult review by Dr. Divya Menon Andersen dated November 13, 2012, states that "inhibition of serum thromboxane B2 (sTxB2) and agonist induced platelet aggregation, the two methods used in this study, are generally appropriate to quantify the anti-platelet activity of acetylsalicylic acid (ASA)" and provides references justifying that conclusion. However, the clinical pharmacology consult also states that "Inhibition of sTxB2 and agonist induced platelet aggregation, the two main methods used to assess anti-platelet effects of ASA in this study, are not sensitive to differences in ASA concentrations at doses above 100 mg" and provides references and data displays from the references justifying this second conclusion. (b) (4)

We agree that the PD assays are not sensitive to differences in ASA concentrations at the dosages used in Study 001. For ease of reference we have reproduced Figure 2 from the OCP review below.

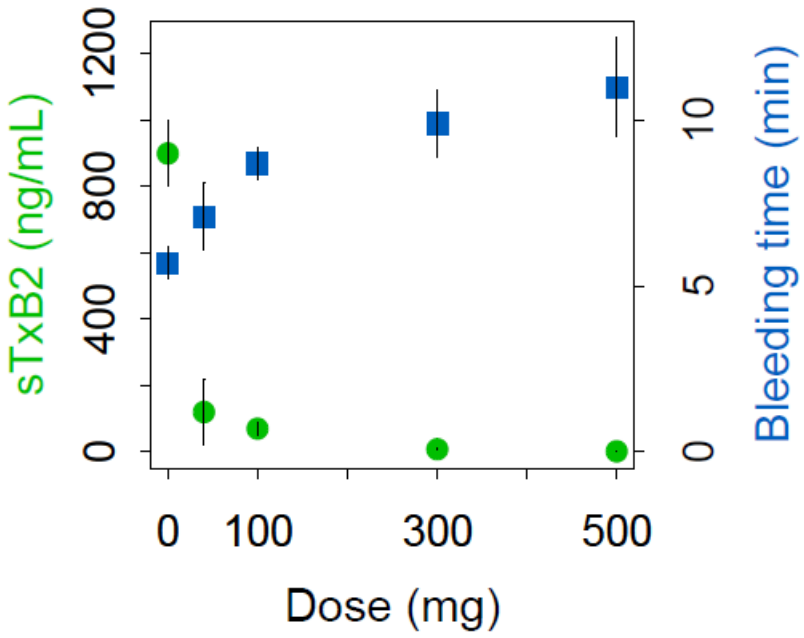

Figure 2 Effect of aspirin (0, 40, 100, 300, and 500 mg) in healthy volunteers on (1) platelet thromboxane B2 (circles) generation 24 hours after oral administration of aspirin and (2) bleeding time (squares) 2 hours after oral administration of asprin. Mean values ± SE are plotted. Adapted from reference # 4.

The results for arachidonic acid-induced platelet aggregation are similar, with both PL2200 and control aspirin showing mean 100% inhibition at six and 24 hours. Our interpretation is that PL2200 does show equivalent PD platelet inhibition effects with these markers at the 325 mg dosage.

However, no one can say with confidence what PD markers track all of the mechanisms by which aspirin achieves its clinical benefits, so an effect of phosphotidyl -choline cannot be excluded.

While the PD results at 325 mg are acceptable regarding the equivalence of the antiplatelet effect of PL2200 at that dosage, they are not informative regarding PD equivalence at lower dosages.

While we cannot extrapolate the PD results to lower dosages, we frequently do extrapolate PK equivalence at higher dosages to lower dosages. However, PL2200 is not strictly bioequivalent to reference aspirin at the 325 mg dosage as shown by the following figure from the OCP review.

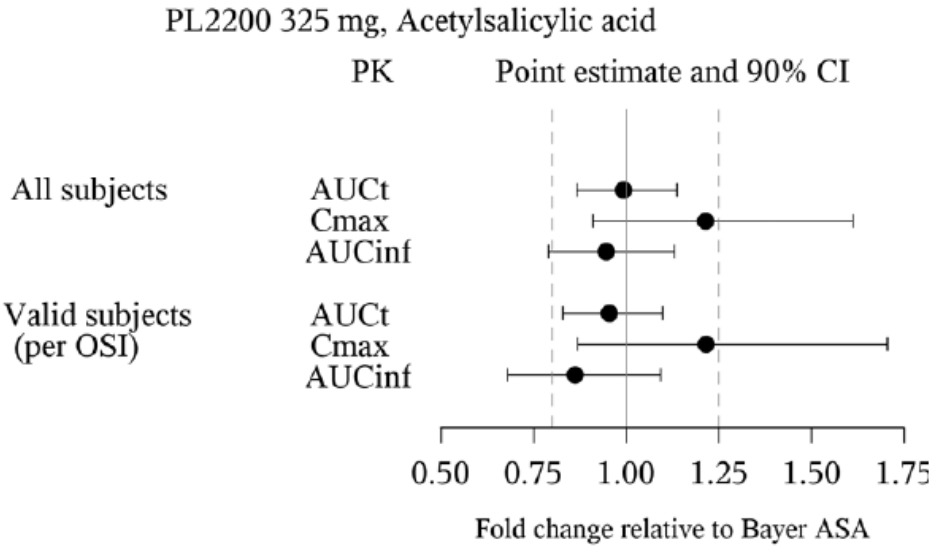

Figure 3 PL2200 meets the BE criteria for AUC 0-4h. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean.

While PL2200 meets the BE criteria for AUC_{0-4h}, it does not meet the usual criteria for C_{max}.

(b) (4)

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/s/

THOMAS A MARCINIAK
11/30/2012

NORMAN L STOCKBRIDGE
11/30/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	November 27, 2012
Reviewer:	Chi-Ming (Alice) Tu, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	(b) (4) (Aspirin) Capsules, 325 mg
Application Type/Number:	NDA 203697
Applicant:	PLx Pharma Inc.
OSE RCM #:	2012-1211

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

Contents

1 INTRODUCTION

This review evaluates the proposed container labels and carton labeling for [redacted] (Aspirin) NDA 203697 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The proposed name [redacted] was found unacceptable in OSE Review# 2012-1210, dated August 17, 2012. The Applicant has not submitted another Request for Proprietary Name as of October 26, 2012.

1.2 REGULATORY HISTORY

Aspirin has been used for pain relief since the early 1800s. Aspirin drug products are regulated under the Over-the-Counter Monographs (Tentative Final Monograph Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use).

The Applicant is seeking approval for Aspirin Capsules (liquid-filled capsules), 325 mg, as a 505(b)(2) application and the reference listed drug is Genuine Bayer® Aspirin Tablets, 325 mg (Monograph drug product).

1.3 PRODUCT INFORMATION

The following product information is provided in the May 17, 2012 proprietary name submission.

- Active Ingredient: Aspirin
- Indication of Use: For the temporary relief of minor aches and pains associated with: a cold, headache, backache, muscular aches, toothache, premenstrual & menstrual cramps, and minor pain of arthritis; temporarily reduces fever.
- Route of Administration: Oral
- Dosage Form: Liquid-filled capsules
- Strength: 325 mg
- Dose and Frequency: Adults and children 12 years and over: take 1 or 2 capsules every 4 hours or 3 capsules every 6 hours; do not exceed 12 capsules in 24 hours.
- How Supplied: 30-count and 120-count bottle in cartons; and 7-count blister in 7-count and 28-count cartons
- Storage: Store at controlled room temperature [redacted]; avoid excessive heat above 40°C (104°F)
- Container and Closure Systems: (Bottles) Round white HDPE bottle, [redacted] closure with [redacted]. (Blister/Carton) [redacted] foil and paper-backed peelable lidding foil.

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following labels and labeling:

- Container Labels submitted May 17, 2012 (Appendix A)
- Carton Labeling submitted May 17, 2012 (Appendix B)

3 RECOMMENDATIONS

The proposed labels and labeling can be improved to increase the readability and prominence of important information on the labels and labeling, DMEPA recommends the following be implemented prior to approval of this NDA:

A. General Comments (for all container labels and carton labeling)

1. Include the word "(NSAID)" in highlighted or in bold type on the PDP per 21 CFR 201.326(a)(2). For example, "Aspirin Capsules, 325 mg (NSAID)" or the word "(NSAID)" can appear after the pharmacologic category such as "Pain Reliever/Fever Reducer (NSAID)".
2. Revise the presentation of the proprietary name to title case instead of the proposed all capitalized letters to improve readability.
3. Remove the statements (b) (4) because there are risks and adverse events associated with your active ingredient as evident in your proposed Warning statements in the Drug Facts.
4. Remove the (b) (4). The proposed indication of use for your product does not include (b) (4)
5. Ensure that the labels and carton labeling for different package sizes have different and unique NDC numbers.

B. Container Label (for Blister only)

1. The information on the blister is illegible. To improve the readability, eliminate the information that can be communicated on the carton labeling so there is space to increase the prominence of pertinent information on this small label per 21 CFR 201.10(i). We recommend the following presentation of information along with your "Peel graphic" on each blister label that contains 1 capsule:

Proprietary name [in title case]

Aspirin Capsules, 325 mg

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Pain Reliever/Fever Reducer

Lot#

Exp

Manufactured by [manufacturer] for [distributor]

[Bar code image]

C. Container Label (for Bottle only), and Carton Labeling (for both Blister and Bottle Container Labeling)

1. Revise the presentation of the statement of pharmacological categories so that it follows the statement of identity – including the proprietary name, if applicable, and the established name – on the principal display panel (PDP) per 21 CFR 201.61. As currently presented, the statement of pharmacological categories precedes the statement of identity. The information should be presented in the following order:

Proprietary name [in title case]

Aspirin Capsules, 325 mg

Pain Reliever/Fever Reducer

If you have further questions or need clarifications, please contact Ermias Zerislassie, OSE project manager, at 301-796-0097.

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

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/s/

CHI-MING TU
11/27/2012

TODD D BRIDGES
11/27/2012

KELLIE A TAYLOR
11/27/2012

CAROL A HOLQUIST
11/27/2012

BOTANICAL INACTIVE INGREDIENTS IN NEW DRUG APPLICATION

BY

BOTANICAL REVIEW TEAM

Application Type:	NDA 505(b)(2)
NDA Number:	203697
Stamp Date:	03-14-2012
Applicant:	PLx Pharma Inc. 8285 El Rio Street, Suite 130 Houston, Texas 77054
DMF #:	N/A (not available)

Drug Name:	(b) (4) (Aspirin) (Formerly: Aspirin PC/PLx2200)
Brand Name:	TBD
Priority Designation:	Standard Review
PDUFA Date:	01-14-2013
Dosage Form:	325 mg capsule
Route of Administration:	Oral
Botanical Raw Material:	(b) (Soybean-derived lecithin (b) (4)
Botanical Drug Substance:	N/A (Note: Aspirin drug substance, acetylsalicylic acid, is highly purified)
Indication(s) requested:	For temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, premenstrual and menstrual cramps; for temporarily reducing fever

Botanical Review Team Reviewer:	Jinhui Dou, Ph.D.
Review Completion Date:	11-16-2012
Botanical Review Team Leader:	Shaw T. Chen, M.D., Ph.D.

New Drug Review Division: Division of Nonprescription Clinical Evaluation

Summary and Recommendations:

This botanical review provides Botanical Review Team (BRT)'s perspective on the quality and safety of Lecithin (b) (4)) which the applicant has specified as (b) (4) in the drug product (PL2200 Aspirin capsules, 325 mg). BRT has identified no safety nor quality issues concerning (b)) which has similar specifications as those listed in the United States Pharmacopeia-National Formulary (USP-NF) lecithin monograph. From BRT's perspective, the use of (b)) as an USP-NF equivalent lecithin is appropriate and does not impact the approvability of the NDA.

BRT Review on Quality of (b) (4) (Lecithin)

The drug product contains an inactive component, (b)) which is a soy-derived lecithin manufactured by (b) (4) (b) (4) As reported in the NDA, (b)) is a phosphatidylcholine-enriched fraction of soy-derived lecithin, containing approximately (b) (4) phosphatidylcholine (PC), one of the major phospholipids) in a (b) (4).

Soy (or soybean), the seeds of *Glycine max* (L.) Merr. in the family of Leguminosae/Fabaceae, and (b) (4) , are the two botanical raw materials involved in the manufacturing of (b)) The key manufacturing steps are illustrated by the applicant in the NDA:

Figure 1. (b) (4)

(b) (4)

The USP-NF Lecithin monograph currently does not include quantitative analysis of phospholipids components. The (b) (4) batches manufactured by the applicant contain, on an average, (b) (4)

(b)) meets the specifications of Lecithin USP-NF monograph (See Table 4 under 3.2.P.4.1 SPECIFICATIONS [SOY LECITHIN] attached at the end of this review).

BRT has communicated with the review team during our internal review meetings, that (b)) can be considered and accepted as an USP-NF equivalent inactive

component (lecithin). From BRT's perspective, additional quality control of the botanical raw materials, i.e., [redacted] and soybean, to assure greater quality and consistency of an inactive ingredient [redacted] is not necessary for this NDA.

BRT Review on Safety of [redacted] (Lecithin)

Each capsule of the Aspirin drug product (PL2200, 325 mg) contains [redacted] For the two major components of [redacted], soy-derived lecithin and [redacted] there are extensive human use experiences with favorable safety profiles when being used as/in food/dietary supplements and excipient in pharmaceutical products. Clinical studies of lecithin in dementia and cognitive impairment patients were summarized in a review article by Higgins JP et al.[1] In the review, the reported doses of lecithin were 10-40 g/day. The percentages of phosphatidylcholine (PC) in the tested lecithin products ranged from low of 22-25%, medium of 53%, to high of 90-95%. The sources of the lecithin were not commented. Soy lecithin (20 g/day) and soy isoflavone protein (25 g/day) were studied for their potential effects on endothelial functions in 25 healthy postmenopausal women for 4 weeks.[2] In animal toxicology studies, phosphatidylinositol (PI), a minor component of [redacted]/soy lecithin, was tested to have no-observed-adverse effect level (NOAEL) of 1,000 mg/kg/day for male and female rats.[3] The calculated safe human equivalent dose of PI will be approximately 10 g/day (for an adult of 60-70 kg).[3]

[redacted] (Lecithin [redacted] as discussed previously, is prepared [redacted]. Those changes, however, will not change the safety profiles of [redacted] from the starting material(s). Since the Aspirin drug product (PL2200, 325 mg) is indicated for temporary relieve of symptoms related to pain and fever, the exposure to soy lecithin [redacted] will usually not exceed [redacted] (i.e., 8 capsule/day). The exposure of [redacted] in terms of the applied doses and durations through the Aspirin product's drug use will be comparable to or lower than that from lecithin's previous human use, including clinical trials of (soy) lecithin and certain marketed soy-lecithin dietary supplement products. [redacted] are regular food ingredients and no safety concerns from their previous human use at the comparable doses of [redacted] used in the aspirin drug product.

Overall, BRT has no safety concern of using [redacted] as an inactive ingredient (i.e., lecithin substitute) in the aspirin drug product (PL2200, 325 mg).

Discussion and Conclusions:

This botanical review provides BRT's perspective on the quality and safety of Lecithin [redacted] the applicant specified [redacted] in the drug product (PL2200 Aspirin capsules, 325 mg).

From BRT's perspective, the characterization and specifications of [redacted] as a botanical derived inactive ingredient is acceptable for the NDA. BRT's review concluded that [redacted] can be considered as a substitute of USP-NF Lecithin for this NDA, because [redacted] meets the specifications of Lecithin USP-NF

monograph. In addition, the changes made by the applicant in the preparation of [redacted] do not alter the safety profiles of soy lecithin.

Because [redacted] is derived from food ingredients and will be used as an inactive ingredient in the drug product, PL2200 (Aspirin capsules, 325 mg); BRT considers that further control of the botanical raw materials (soybean and [redacted]), beyond the requirements for food or inactive ingredients in drug products, is unnecessary.

For NDA safety and quality review of the drug product (PL2200 Aspirin capsules, 325 mg), please refer to the multi-disciplinary reviews from the DNCE division, clinical pharmacology, and ONDQA.

References:

1. \Higgins JP, Flicker L. Lecithin for dementia and cognitive impairment. Cochrane Database Syst Rev. 2003;(3):CD001015.
2. Evans M, Njike VY, Hoxley M, Pearson M, Katz DL. Effect of soy isoflavone protein and soy lecithin on endothelial function in healthy postmenopausal women. Menopause. 2007 Jan-Feb;14(1):141-9
3. Honda K, Enoshima T, Oshikata T, Kamiya K, Hamamura M, Yamaguchi N, Nakamura K, Oguma Y, Fujiwara S, Takabe M, Sono A, Kawasaki T, Nasu M, Otsubo K, Wakigawa K. Toxicity studies of Asahi Kasei PI, purified phosphatidylinositol from soy lecithin. J Toxicol Sci. 2009 Jun;34(3):265-80.

Attachment 1 (Copied from NDA 3.2.P.4.1, Module 3, Page 5 of 6)

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(b) (4)

(b) (4)

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/s/

JINHUI DOU
11/19/2012

SHAW T CHEN
11/19/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date: November 19, 2012

From: Alyson Karesh, MD, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, MD, Team Leader
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, MD, Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Nonprescription Clinical Evaluation (DNCE)

NDA: 203697

Drug: Aspirin Capsules, 325 mg

Date of Internal Meeting: November 7, 2012

Proposed Indications (12 years of age and older): OTC use for

(1) the temporary relief of minor aches and pains associated with cold, headache, backache, muscular aches, toothache, premenstrual and menstrual cramps, and minor pain of arthritis
(2) to temporarily reduce fever

Consult Request[1]**:** The Division of Nonprescription Clinical Evaluation (DNCE) requested Pediatric and Maternal Health Staff (PMHS) input on the sponsor's request for a full waiver under PREA. (See Appendix I for excerpts from the PMHS Request for Consultation form, October 2, 2012, for details.)

[1] Pediatric and Maternal Health Staff Request for Consultation, Aspirin Capsules, 325 mg, October 2, 2012.

Background
The sponsor has submitted an NDA (203697) for Aspirin Capsules to be approved under the 505(b)(2) pathway with Genuine Bayer Aspirin tablets as the Reference Listed Drug. Although the sponsor is requesting a "full waiver", their proposed labeling is for patients 12 years and older. The sponsor believes a "full waiver" is appropriate because, per the sponsor, their product does not provide a meaningful benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. With their waiver request the sponsor included articles to support their assertions that due to Reye Syndrome concerns, aspirin is not widely used by pediatric patients.

(b) (4), (b) (5)

DNCE requested PMHS input on the sponsor's proposed pediatric waiver.

Summary
PMHS participated in an internal meeting with DNCE to discuss the sponsor's "full-waiver" request. DNCE will reinvestigate whether the proposed aspirin product would trigger PREA. If PREA is triggered, DNCE and PMHS agreed that a full waiver would be appropriate:

- For the indication, "temporary relief of minor aches and pains associated with cold, headache, backache, muscular aches, toothache, premenstrual and menstrual cramps, and minor pain of arthritis", a full waiver would be appropriate because the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.
  Reviewer's comment: Based on the data submitted by the sponsor, use of aspirin products is low and other therapies such as ibuprofen and acetaminophen are preferred.

- For the indication, "to temporarily reduce fever", a full waiver would be appropriate because there is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric age groups, in this case, due to the Reye Syndrome risk. The reason for the safety-related waiver will need to be included in labeling.
  Reviewer's comment: The safety concern applies to all pediatric age groups and is not simply a concern for younger children. A brief PMHS literature review revealed that although the risk of Reye syndrome decreases with age, Reye

2 (b) (5)
3
(b) (5)

syndrome cases do still occur in adolescents. For example, one article stated that 8 percent of Reye syndrome cases occur in children 15 to 17 years of age.[4]

If a full waiver is granted, the product would not be labeled for use in patients 12 years of age and older as the sponsor proposed.

If PREA is triggered, DNCE will present their proposal to grant a full waiver to the Pediatric Review Committee (PeRC) on December 19, 2012. PMHS expressed to DNCE a willingness to provide advice, including help with the PeRC paperwork, in the future if needed.

December 19, 2012 Addendum

DNCE concluded that PREA would not be triggered and that product labeling, including pediatrics, will be consistent with other already approved aspirin products. Therefore, this product will be approved for use by individuals 12 years and older.[5]

[4] Beutler AI, et al. FPIN's Clinical Inquiries, Aspirin use in children for fever or viral syndromes. *American Academy of Family Physicians*. 2009; 80(12):1473-4

[5] (b) (5)

APPENDIX I
Excepts for the PMHS Request for Consultation Form for Aspirin Capsules, October 2, 2012[6]

"1. Please briefly describe the submission including drug's indication(s):
Indication: Temporary relief of minor aches and pains associated with a cold, headache, backache, toothache, premenstrual and menstrual cramps, and minor pain of arthritis; and temporarily reduces fever.

The Sponsor PLx Pharma has submitted NDA 203697 for PL2200 Aspirin Capsules, 325 mg, an immediate release formulation containing a lipidic ((b) (4)) suspension of aspirin for oral administration. This is a 505(b)(2) application with Genuine Bayer Aspirin tablets as the reference drug. The Sponsor is requesting OTC monograph fever and pain indications and would like to label the product for those aged12 and above. The Agency told the Sponsor that the NDA should provide evidence that the lipidic suspension does not affect the pharmacokinetics (PK) or pharmacodynamics (PD) of aspirin.

The Sponsor is requesting a full waiver for all pediatric age groups for the above indications because PL2200 does not provide a meaningful benefit over existing therapies in pediatric patients and is not likely to be used in a substantial number of them. The monograph is not final for fever and pain indications. The Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the Counter Human Use Tentative Final Monograph (TFM) lists dosing for children down to the age of 2 yrs. There is however professional labeling which has been finalized for vascular indications and rheumatologic disease indications. Dosing for juvenile rheumatoid arthritis starts at 90-130 mg/kg/day in divided doses, with increases as needed for an anti-inflammatory effect with target plasma salicylate levels of 150-300 mdg/mL."

"2. Describe in detail the reason for your consult. Include specific questions:
We would like your help in answering should we grant a full waiver."

[6] Pediatric and Maternal Health Staff Request for Consultation, Aspirin Capsules, 325 mg, October 2, 2012.

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/s/

ALYSON R KARESH
01/24/2013

HARI C SACHS
01/25/2013
I agree with these recommendations.

LYNNE P YAO
01/30/2013

M E M O R A N D U M

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

DATE: October 31, 2012

TO: Andrea Leonard-Segal, M.D., M.S.
Director,
Division of Nonprescription Clinical Evaluation,
Office of Drug Evaluation IV

FROM: Jyoti B. Patel, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 203-697, Aspirin Capsules sponsored by PLx Pharma Inc.

At the request of the Division of Nonprescription Clinical Evaluation, the Division of Bioequivalence and GLP Compliance (DBGLPC), conducted audits of the clinical and analytical portions of the following bioequivalence studies:

Study Number: PL-ASA-001
Study Title: "A randomized, actively controlled, crossover bioequivalence study of Aspirin-PC (ASA-PC) versus Aspirin (ASA) in healthy volunteers"

Study Number: PL-ASA-003
Study Title: "A randomized, actively controlled, crossover food-effect study of PL2200 in healthy volunteers"

The inspected studies were conducted to assess the safety, food effect, and bioequivalence of the test product Aspirin capsule, 325 mg (ASA-PC; PL2200) and the reference product Bayer® Aspirin tablet, 325 mg by pharmacokinetic analysis of acetyl salicylic acid (ASA) and salicylic acid (SA) concentrations in plasma. In addition, anti-platelet pharmacodynamic bioequivalence between the test and reference products were evaluated by determining the serum Thromboxane B_2 concentrations (inhibition of serum Thromboxane B_2).

The FDA audits of the clinical and analytical portions of the above studies were conducted at Houston Institute for Clinical Research, Houston, TX (June 4-7, 2012) by Darla J. Christopher (ORA, Dallas District Office), and at (b) (4) (b) (4) and OSI scientist Jyoti B. Patel, respectively. The audits included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firms' management and staff. **Audit of the analytical data revealed that (b) (4) had initially performed bioanalytical method validation of the analysis of ASA and SA in 2007. The sponsor has submitted this validation report and data to the Agency; however, (b) (4) revalidated the bioanalytical method for analysis of ASA and SA in 2011 and 2012. The new validation report (Attachment 3) and data have not been submitted yet to the Sponsor or Agency.**

Following the inspections, there were no significant observations at the clinical site and no Form FDA-483 was issued; however, a Form FDA-483 was issued at the analytical site (b) (4)

Please note that OSI has received (b) (4) initial response; however, this is not a complete response. (b) (4) plans to perform a partial method revalidation for ASA and SA, and submit the completed results to the Sponsor and Agency by November 30, 2012.

The Form FDA-483 observations (Attachment 1), (b) (4) response (Attachment 2), and OSI's evaluation of the observations follow.

Analytical site: (b) (4)

1. **Failure to document all aspects of sample storage and handling (i.e. maintaining specimen tracking log) during conduct of Study PL-ASA-001. Specifically, for the following:**

a) Samples (plasma, serum, and urine) received on 2-19-2008, 2-20-2008, 2-27-2008, 3-5-2008, 3-12-2008, and 3-14-2008.
b) Plasma samples during analysis of plasma Acetylsalicylic Acid (ASA) and Salicylic Acid (SA) in runs AsaJ09, AsaJ10, AsaJ13, AsaJ16, and AsaJ17; serum samples during analysis of serum Thromboxane B2 in runs TBXG01, TBXG01a, TBXG02, TBXG04, and TBXG08.
c) QC samples during analysis of plasma ASA, SA, and serum Thromboxane B2.

(b) (4) agreed with the observation that the information on the "Specimen Tracking Log" was not consistently and completely documented for Study PL-ASA-001 in 2008. The sample receipt process was improved in April 2009 and employees have been retrained. The improvement was in effect at the time of Study PL-ASA-003 (2010-2011), for which specimen tracking was consistently documented. (b) (4) acknowledged that specific entries for transfers to and from the freezers were missing from the "Specimen Tracking Logs"; however, the firm provided assurance that the samples and QCs were stored at -80^{0}C based on the following:

1. Documentation on the "Specimen Receipt Log" for the initial storage of samples
2. Sample worklist for each analytical run generated from the (b) (4) system
3. Verification of samples stored at -80^{0}C during sample inventory performed on August 20, 2009 as part of sample disposition process
4. All the QCs were stored in a single freezer according to the SOP

Evaluation:
The information of sample storage at -80^{0}C was verified using alternate source documents. The above observation is not likely to impact the quality of the study data.

2. Failure to document all aspects of sample processing during validation study of ASA and SA. Specifically, adequate information was not documented for processing of calibration standards and QCs during evaluation of "Processed Batch Stability"/"Autosampler Reproducibility" (3 days at room temperature).

(b) (4) agreed that the initial bioanalytical method validation of ASA and SA done in 2007 lacked adequate sample processing documentation, and the method revalidation performed in 2011

does not fully replicate the time frame and storage conditions of the processed subject samples stored for 3 days at room temperature before re-injection for analysis. (b) (4) **plans to perform partial revalidation to further investigate processed batch stability. The results are expected to be available by November 30, 2012 and will be submitted to the sponsor and agency.**

Evaluation:
The data for the following re-injected runs for ASA and SA (Attachment 4) are not considered reliable pending the submission by (b) (4) of revalidated results for "Processed Batch Stability"/"Autosampler Reproducibility" (3 days at room temperature) and review by the Agency:

Study PL-ASA-001

- **Run# 7, Batch AsaJ05a (subjects: 102, 105, 126)**
- **Run# 23, Batch AsaJ15b (subject: 116)**

Study PL-ASA-003

- **Run# 8, Batch Sal31r1 (subjects: 007, 008) for SA only**

3. **Failure to have a confirmatory step (e.g., by balance printer or witness initials) for the reference material weighing used in the preparation of calibration standard and QC stock solutions.**

(b) (4) agreed with the observation that balance printout or witness signature was not available to confirm reference weighing. The stock solutions were confirmed against a second stock solution from an independent mass weighing prior to use in method validation or sample analysis.

Evaluation:
The balance was mostly used to weigh reference ASA powder (10 mg) for preparation of stock solution. Reference materials for SA, Thromboxane B2, and internal standards were either in liquid form or pre-weighed powder obtained from the supplier, which were entirely used to make the respective stock solutions. Independent stock solutions were prepared for calibration standards and quality controls (QCs). The above observation is not likely to impact the quality and integrity of study data.

Conclusions:

Following the review and evaluation of the EIR (clinical), Form FDA-483 observations (analytical) and (b) (4) initial response, the reviewers are of the opinion that the clinical data generated for studies PL-ASA-001 and PL-ASA-003 are acceptable for further agency review; however, not all analytical data are acceptable at this time. The analytical data for subjects 102, 105, 126 and 116 (ASA and SA) from Study PL-ASA-001, and subjects 007 and 008 (SA only) from Study PL-ASA-003 are not considered reliable pending review of revalidation data by the Agency. These data are expected to be submitted by November 30, 2012.

Jyoti B. Patel, Ph.D.
DBGLPC, OSI

Final Classifications:
NAI: Clinical site: Houston Institute for Clinical Research, Houston, TX
FEI: 3005043134

VAI: Analytical site: (b) (4)

CC:
CDER OSI PM TRACK
OSI/DBEGLPC/Taylor/Haidar/Dejernett/Patel/Mada/CF
ODE IV/DNCE/Leonard-Segal/Adams-King
OTS/OCP/DCP II/Naraharisetti
HFR-SW1580/Christopher, Darla J/Cheney, Sean
HFR-SW150/Turcovski
HFR-CE850/Bigham
HFR-CE8590/Singh
Draft: JBP 10/15/2012
Edit: SHH 10/30/2012; WHH 10/31/2010
OSI File BE# 6335; O:\BE\EIRCOVER\203697.plx.asp.doc
FACTS: **1405234**

ATTACHMENTS:
1. **Form FDA-483**
2. (b) (4) **response**
3. **Bioanalytical method validation report (2011, 2012) for ASA, SA, and Thromboxane B2 along with Long term stability,**
4. **Analytical run summary for analysis of plasma ASA and SA from studies PL-ASA-001 and PL-ASA-003**

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/s/

JYOTI B PATEL
10/31/2012

SAM H HAIDAR
10/31/2012

WILLIAM H TAYLOR
10/31/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 203697 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: aspirin Dosage Form: capsule Strengths: 325 mg		
Applicant: PLx Pharma Inc. Agent for Applicant (if applicable):		
Date of Application: March 12, 2012 Date of Receipt: March 14, 2012 Date clock started after UN:		
PDUFA Goal Date: January 14, 2013	Action Goal Date (if different):	
Filing Date: May 12, 2012	Date of Filing Meeting: April 30, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 2		
Proposed indication(s)/Proposed change(s):		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☒ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***		X		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***			X	
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]				

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 09/23/10 ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 12/16/11 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 30, 2012

BLA/NDA/Supp #: 203697

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: aspirin capsule, 325 mg

DOSAGE FORM/STRENGTH: capsule, 325 mg

APPLICANT: PLx Pharma Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: PLx Pharma Inc. submitted a 505(b)(2) NDA for a new 325 mg aspirin capsule formulation. This product would be marketed under the proposed tradename (b) (4) Reference is made to OTC Bayer Aspirin, 325 mg for clinical safety and efficacy. A Pre-NDA meeting was held with PLx on December 16, 201 to discuss the content of the NDA submission.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	James Lee	Y
	CPMS/TL:	Melissa Furness	Y
Cross-Discipline Team Leader (CDTL)	Daiva Shetty		Y
Clinical	Reviewer:	Priscilla Callahan-Lyon	Y
	TL:	Daiva Shetty	Y
Social Scientist Review (*for OTC products*)	Reviewer:	Barbara Cohen	Y
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	Elaine Abraham	Y
	TL:	Steve Adah	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Suresh Naraharsetti	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Cindy Li	Y
	TL:	Paul Brown	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Muthukumar Ramaswamy	Y
	TL:	Ali Al Hakim	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Todd Bridges	N
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Tien Mien Chen – Biopharm Reviewer Jinhui Dou – Botanicals Reviewer		Y
Other attendees	Frank Pucino, DAAAP		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Joel Schiffenbauer **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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/s/

JAMES C LEE
06/15/2012

BOTANICAL INACTIVE INGREDIENTS IN NEW DRUG APPLICATION

BY

BOTANICAL REVIEW TEAM

Application Type:	NDA 505(b)(2)
NDA Number:	203697
Stamp Date:	03-14-2012
Applicant:	PLx Pharma Inc. 8285 El Rio Street, Suite 130 Houston, Texas 77054
DMF #:	N/A (not available)

Drug Name:	(b) (4) (Aspirin) (Formerly: Aspirin PC/PLx2200)
Brand Name:	TBD
Priority Designation:	Standard Review
PDUFA Date:	01-14-2013
Dosage Form:	325 mg capsule
Route of Administration:	Oral
Botanical Raw Material:	(b) (Soybean-derived lecithin (b) (4)
Botanical Drug Substance:	N/A (Note: Aspirin drug substance, acetylsalicylic acid, is highly purified)
Indication(s) requested:	For temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, premenstrual and menstrual cramps; for temporarily reducing fever

Botanical Review Team Reviewer:	Jinhui Dou, Ph.D.
Filing Review Completion Date:	05-17-2012
Botanical Review Team Leader:	Shaw T. Chen, M.D., Ph.D.

New Drug Review Division: Division of Nonprescription Clinical Evaluation

Summary and Filling Recommendation:

This botanical review provides Botanical Review Team (BRT)'s perspective on the quality and safety of Lecithin [redacted] which the sponsor has specified as [redacted] in the drug product (PL2200 Aspirin capsules, 325 mg). BRT has identified no filing issues concerning [redacted] and the NDA is acceptable for filing.

BRT Filing Review Notes on Quality of [redacted] (Lecithin)

One of the inactive components of the proposed drug product is a soy-derived lecithin, [redacted] manufactured by [redacted] is a phosphatidylcholine-enriched fraction of soy-derived lecithin, containing approximately [redacted] phosphatidylcholine (PC), one of the major phospholipids) in a [redacted] The key manufacturing steps are illustrated by the sponsor in the NDA:

Figure 1 [redacted] Composition and Production Process Overview

[redacted]

The USP-NF Lecithin monograph currently does not include quantitative analysis of phospholipids components. The [redacted] batches manufactured by the sponsor contain, on an average, [redacted] meets the USP specifications of Lecithin NF monograph (See Table 4 under 3.2.P.4.1 SPECIFICATIONS [SOY LECITHIN] attached at the end of this review).

BRT Review Notes on Safety of [redacted] (Lecithin)

Each capsule of the Aspirin drug product (PL2200, 325 mg) contains [redacted] of [redacted] For the two major components of [redacted] soy-derived lecithin [redacted], there are extensive human use experiences with favorable safety profiles when being used as/in food/dietary supplements and excipient in pharmaceutical products. Clinical studies of lecithin in dementia and cognitive impairment patients were summarized in a review article by Higgins JP et al..[1] In the review, the reported doses of lecithin were 10-40 g/day. The percentages of phosphatidylcholine (PC) in the tested lecithin products ranged from low of 22-25%, medium of 53%, to high of 90-95%. The

sources of the lecithin were not commented. Soy lecithin (20 g/day) and soy isoflavone protein (25 g/day) were studied for their potential effects on endothelial functions in 25 healthy postmenopausal women for 4 weeks.[2]

(b) (Lecithin with (b) (4)), as discussed previously, is prepared (b) (4) (b) (4) Those changes, however, will not change the safety profiles of (b) (4) from the starting material(s). Since the Aspirin drug product (PL2200, 325 mg) is indicated for temporary relieve of symptoms related to pain and fever, the exposure to soy lecithin (b) will usually not exceed (b) (4) (i.e., 8 capsule/day). The exposure of (b) (4) in terms of the applied doses and durations through the Aspirin product's drug use will be comparable to or lower than that from lecithin's previous human use, including clinical trials of (soy) lecithin and certain marketed soy-lecithin dietary supplement products.

Discussion and Conclusions:

For safety and quality of the drug product (PL2200 Aspirin capsules, 325 mg), please refer to the multi-disciplinary reviews from the DNCE division, clinical pharmacology, and ONDQA. This botanical review provides BRT's perspective on the quality and safety of Lecithin (b) (4) the sponsor specified (b) (4) in the drug product (PL2200 Aspirin capsules, 325 mg).

From BRT's perspective, the characterization and specifications of (b) (4) as a botanical derived inactive ingredient is acceptable for filling of the NDA. BRT's preliminary review concluded that (b) (4) can be considered as an equivalent substitute for USP-NF Lecithin for this NDA, because (b) (4) meets the specifications of Lecithin USP-NF Monograph. In addition, the changes made by the sponsor in the preparation of (b) (b) (4) do not alter the safety profiles of soy lecithin.

Because (b) (4) is derived from food ingredients and will be used as an inactive ingredient in the drug product, PL2200 (Aspirin capsules, 325 mg); BRT considers that further control of the botanical raw materials (soybean and (b) (4)) is unnecessary.

References:

1. Higgins JP, Flicker L. Lecithin for dementia and cognitive impairment. Cochrane Database Syst Rev. 2003;(3):CD001015.
2. Evans M, Njike VY, Hoxley M, Pearson M, Katz DL. Effect of soy isoflavone protein and soy lecithin on endothelial function in healthy postmenopausal women. Menopause. 2007 Jan-Feb;14(1):141-9.

Attachment 1 (Copied from NDA 3.2.P.4.1, Module 3, Page 5 of 6)

Table 4. Comparison of the Lecithin NF Monograph and Proposed (b) (4) Specifications for Release into PL2200 Production

Test	Lecithin NF USP Method	Lecithin NF USP Acceptance Criteria	Proposed PLx Method	Proposed PLx Acceptance Criteria
(b) (4)				

[1] (b) (4) from the supplier's Certificate of Analysis will be used as a basis for release for PL2200 production. Validation for these test methods are supported by DMF (b) (4)

[2] The range was set based upon the mean and ±2.5 SD of the batches manufactured to date. This range will be adjusted following further experience with more (b) (4) use in the production of PL2200.

[3] Calculated.

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/s/

JINHUI DOU
05/17/2012

SHAW T CHEN
05/17/2012

Filing Review for PL2200 Aspirin Capsules

SUBMISSION DATES:	March 12, 2012
NDA/SUBMISSION TYPE:	203697 (PA)
ACTIVE INGREDIENTS:	Aspirin 325 mg
DOSAGE FORMS:	Capsule
SPONSOR:	PLx Pharma Inc. 8285 El Rio Street, Suite 130 Houston, Texas 77054 Jason E. Moore Vice President (713) 842-1249
REVIEWER:	Elaine Abraham RPh
TEAM LEADER:	Steven Adah PhD

Submitted Labeling	Representative of Following SKUs
30-count bottle and carton	N/A
120-count bottle and carton	N/A
7-count blister card	N/A
7-count blister carton	N/A
28-count blister carton	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	Yes	PA for new NDA
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	No	N/A
Is distributor labeling included?	No	N/A
Does the submission include the annotated specifications for the Drug Facts label?	Yes	Annotated specifications are incomplete
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include "prescription strength" or similar statements?	No	
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	Yes	The trade name (b) (4) is being reviewed by DMEPA
Does a medical officer need to review any clinical issues?	Yes	New NDA
If SLR, should ONDQA also review?	Yes	New NDA

Reviewer's comment: The submission contains incomplete annotated specifications for Drug Facts. For example, there is a general specification for all headings, rather than listing font size for "Drug Facts", "Drug Facts (continued)", headings and subheadings. Text size is listed but not bullet size. Leading (space between lines) is not listed.

Information Request: Request complete annotated font specifications for Drug Facts in the 74-day letter.

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/s/

ELAINE E ABRAHAM
05/07/2012

STEVEN A ADAH
05/07/2012