CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203697Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT CERTIFICATION

The Federal Food, Drug, and Cosmetic Act ("FDC Act") and FDA's implementing regulations require each NDA sponsor to submit with its application "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the [NDA] or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."
FDC Act 505(b)(1); see 21 CFR 314.53(b)(1).

PLx Pharma Inc. hereby submits with this NDA 203697 the FDA 3542a Form for each of the following U.S. patents that meet the FDA Orange Book listing criteria:

US #5,763,422: Methods of enhancing the therapeutic activity of NSAIDs and combinations of zwitterionic phospholipids useful therein.

Expiration Date of Patent #5,763,422: June 9, 2015

Jason E. Moore, MS, MBA, RAC
Vice President

02-FEB-2012
Date

Department of Health and Human Services
Food and Drug Administration

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

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

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
203697

NAME OF APPLICANT/NDA HOLDER
PLx Pharma Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)
PRINADAY

ACTIVE INGREDIENT(S)	STRENGTH(S)
Aspirin	325 mg

DOSAGE FORM
capsule, liquid filled

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

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

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

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

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,763,422	June 9, 1998	June 9, 2015

d. Name of Patent Owner
The University of Texas Board of Regents

Address *(of Patent Owner)*
Ashbel Smith Hall, Suite 820, 201 West 7th St.

City/State
Austin, TX

ZIP Code	FAX Number *(if available)*
78701	(512) 499-4425
Telephone Number	E-Mail Address *(if available)*
(512) 499-4402	bor@utsystem.edu

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

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

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	E-Mail Address *(if available)*

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Jason Moore	02-FEB-2012

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

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Jason E Moore, MS, MBA, RAC, Vice President, PLx Pharma Inc.	
Address: 8285 El Rio, Suite 130	City/State: Houston, TX
ZIP Code: 77054	Telephone Number: 713-842-1249
FAX Number *(if available)*: 713-842-3052	E-Mail Address *(if available)*: jason.moore@plxpharma.com

EXCLUSIVITY SUMMARY

NDA # 203697 SUPPL # HFD#560

Trade Name

Generic Name aspirin

Applicant Name PLx Pharma

Approval Date, If Known January 14, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒* NO ☐

*Efficacy Literature

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒* NO ☐

*Relied on literature that supported Final Monograph, which includes instruction on safety of professional labeling. Sponsor relied on additional safety and efficacy literature as well.
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21317
(Discontinued)
NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒* NO ☐

*Aspirin-PC is an immediate release oral drug product consisting of 325-mg of aspirin USP (active ingredient), with (b) (4) of lecithin and other excipients. The Sponsor conducted two PK studies and relied on the safety and efficacy of aspirin based on literature references and the final monograph for aspirin to support this NDA. (b) (4)

The basis for requesting exclusivity for Aspirin-PC as outlined by the Sponsor is reproduced below:

- No drug product containing 325 mg aspirin with the same conditions of approval has been previously approved under a new drug application.
- One new clinical investigation included in this application was conducted on humans, and meets the definition of "a new clinical investigation" set forth in 21 CFR 341.108(a). PLx certifies that any such investigation has not been used by the Agency as part of the basis for a finding of substantial evidence of effectiveness for any previously approved new drug application or supplement.

The new clinical investigation included in this application that is essential for approval meets the definition of "essential to approval" set forth in 21 CFR 341.108(a). The clinical investigation was sponsored by PLx Pharma under IND 074290, and is Study No. PL-ASA-001: "A Randomized, Actively Controlled, Cross-over Bioequivalence Study of Aspirin-PC (ASA-PC) versus Aspirin in Healthy Volunteers"

**

As an additional piece of information, the NDA submission noted that there was a single ingredient aspirin product on the market listed in the Orange Book (a tablet containing 500 mg aspirin). The Orange Book does verify that NDA 21317 was approved in 2001 for *Bayer Extra Strength Aspirin for Migraine Pain* and has since been discontinued.

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

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

other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☐ NO ☒*

*The sponsor submitted a clinical pharmacology (bioequivalence) study (see response to Part III #1).

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

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

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

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Janice Adams-King, RN, BSN, MS
Title: Sr RPM
Date: 2/4/13

Name of Office/Division Director signing form: Joel Schiffenbauer, M.D.
Title: Deputy Director, Division of Nonprescription Clinical Evaluation

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

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

/s/

JANICE ADAMS
02/05/2013

JOEL SCHIFFENBAUER
02/05/2013

DEBARMENT CERTIFICATION

PLx Pharma Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

PLx reviewed the FDA Debarment List (Drug Product Applications), accessed on 13 January 2012 at http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm and provided below, to verify that none of our employees or contractors is presently debarred.

Also provided are debarment statements from key persons involved in the preparation of this application:

(b) (4)

Jason E. Moore, MS, MBA, RAC
Vice President

25-JAN-2012
Date

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

From: Jason Moore [mailto:Jason.Moore@plxpharma.com]
Sent: Thursday, January 03, 2013 2:02 PM
To: Adams-King, Janice
Subject: RE: NDA 203697 Labeling Changes Requested

Hi Janice,

Happy New Year! I am acknowledging your email, and will make the requested changes; I anticipate that we will be able to meet the required timeline.

To confirm, you consider the established name to be "(b) (4)" (or simply "Aspirin")? We have considered the nonproprietary established name to be "(b) (4) based on our NDA communications, which would not be marketed, as reflected in our last labeling submission. We prefer the latter; is that ***un***acceptable? Can you offer some explanation/clarification, please?

Thanks!
Jason

Jason E. Moore, MS, MBA, RAC
Vice President
PLx Pharma Inc.
8285 El Rio Street, Suite 130
Houston, TX 77054
713-842-1249 x207; (b) (6)
Fax: 713-842-3052
jason.moore@plxpharma.com
www.plxpharma.com

From: Adams-King, Janice [mailto:Janice.Adams-King@fda.hhs.gov]
Sent: Thursday, January 03, 2013 12:40 PM
To: Jason Moore
Subject: NDA 203697 Labeling Changes Requested
Importance: High

Hi Jason, Please see our labeling comments below and provide the updated labeling no later than Monday, January 7. Should you be unable to meet this deadline, please let me know the earliest date you can have the updated labeling to us. Thank you, Janice

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)

(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).)

CAPT Janice Adams-King, RN, BSN, MS (USPHS)
Regulatory Health Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV, CDER/FDA
10903 New Hampshire Avenue, Bldg. 22, Room 5408
Silver Spring, MD 20993
Phone: 301-796-3713 Fax: 301-796-9899
Janice.Adams-King@fda.hhs.gov

From: Jason Moore [mailto:Jason.Moore@plxpharma.com]
Sent: Friday, November 02, 2012 6:44 PM
To: Adams-King, Janice
Subject: RE: Information Request: NDA 203697/Aspirin

Hi Janice,

As requested, please find attached the Case Report Form for PL-ASA-001 Subject 123.

Also, you asked for clarification on whether there is any documented record stating subjects 123 and 126 were mis-dosed in the study. We did previously investigate this with the site at the time the outlier values were noted at the conclusion of the PL-ASA-001 study, as these values suggested the potential for mis-dosing. We determined at that time, and during a subsequent review, that there was no evidence of mis-dosing in the clinical documentation.

We will plan to also submit this response to the NDA via the CDR, unless you advise otherwise. Of course, please let me know if you have any additional questions.

Warm regards,
Jason

Jason E. Moore, MS, MBA, RAC
Vice President
PLx Pharma Inc.
8285 El Rio Street, Suite 130
Houston, TX 77054
713-842-1249 x207 (b) (6)
Fax: 713-842-3052
jason.moore@plxpharma.com
www.plxpharma.com

From: Adams-King, Janice [mailto:Janice.Adams-King@fda.hhs.gov]
Sent: Thursday, November 01, 2012 2:18 PM
To: Jason Moore
Subject: Information Request: NDA 203697/Aspirin
Importance: High

Good Afternoon Jason, Please see the information request below and respond via e-mail by COB Monday, November 6, 2012 and provide an official response to the application. Thank you, Janice

In your recent response dated 10/10/2012 you indicated that subjects126 (325 mg) and 123 (650 mg) are outliers and need to be excluded from the analysis. We notice that you have submitted case-report form for subject 126 along with subject 115 in your response dated 07/13/2012. Provide case-report-form for subject 123. Also clarify if there is any documented record stating subjects 123 and 126 were mis-dosed in the study.

CAPT Janice Adams-King, RN, BSN, MS (USPHS)
Regulatory Health Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV, CDER/FDA
10903 New Hampshire Avenue, Bldg. 22, Room 5408
Silver Spring, MD 20993
Phone: 301-796-3713 Fax: 301-796-9899
Janice.Adams-King@fda.hhs.gov

From: Jason Moore [mailto:Jason.Moore@plxpharma.com]
Sent: Thursday, October 25, 2012 11:24 AM
To: Adams-King, Janice
Subject: RE: Assay methods for NDA 203697 (ASA/PC)

Hi Janice,

I wanted to send this response along to you; sorry it's taken several days longer than I had hoped. We are preparing a revised clinical study report for PL-ASA-001, to reflect the recent clinical pharmacology data update (addressing the statistical programming errors), so the information below will be incorporated into that CSR revision. Do you need me to prepare an information amendment to the NDA with this correspondence (given the planned CSR revision)? Happy to do that if that is what is needed. We can discuss when we speak later today.

FDA Request 22 Oct 2012

"It is not clear to us what data are presented under section 14.2.6 and in the analysis dataset plateagg.xpt. Are these % platelet aggregation or as you have labeled it arachidonic acid levels? Also, please provide details of the method used to generate these data".

PLx Pharma Response

Upon review of the Tables in Section 14.2.6, we recognize the inconsistency and confusing nature of Table 14.2.6.1, in light of the other tables in Section 14.2.6 and the SAS data files sent to the Agency. We have investigated and determined that the variables were incorrectly labeled. We have relabeled the variables in Section 14.2.6 to accurately identify that this data represents percent platelet aggregation induced either by arachidonic acid or collagen. The following table provides a summary of the revisions and links to the dataset "plateagg.xpt" variables for ease of review associated with Table 14.2.6.1.

Variable Names in Table 14.2.6.1 (CSR 001, p. 458-459 [650mg dose] and 460-461 [325 mg dose] of 612).

Initial Variable Name/ Units	Dataset = plateagg / variable name	Corrected Variable Name/Units	Data Listings Table/ for the reference variables
BASELINE ARACHIDONIC ACID (mg/mL)	BL_AA	Baseline Arachidonic Acid-induced Platelet Aggregation (%)	
ARACHIDONIC ACID (mg/mL) 6 HOURS POST	HR6_AA	Arachidonic Acid-induced Platelet Aggregation at 6 hours Post Treatment (%)	
ARACHIDONIC ACID (mg/mL) 24 HOURS POST	HR24_AA	Arachidonic Acid-induced Platelet Aggregation at 24 hours Post Treatment (%)	
% INHIBITION IN ARACHIDONIC ACID 6 HOURS POST	INH6_AA	% Inhibition of Arachidonic Acid-induced Platelet Aggregation at 6 hours Post Treatment	Table 14.2.6.2.1 [325 mg dose] Table 14.2.6.2.2 [650 mg dose]
% INHIBITION IN ARACHIDONIC ACID 24 HOURS POST	INH24_AA	% Inhibition of Arachidonic Acid-induced Platelet Aggregation at 24 hours Post Treatment	Table 14.2.6.2.3 [325 mg dose] Table 14.2.6.2.4 [650 mg dose]
BASELINE COLLAGEN (/mL)	BL_CO	Baseline Collagen-induced Platelet Aggregation (%)	
COLLAGEN (/mL) 6 HOURS POST	HR6_CO	Collagen-induced Platelet Aggregation at 6 hours Post Treatment (%)	

COLLAGEN (/mL) 24 HOURS POST	HR24_CO	Collagen-induced Platelet Aggregation at 24 hours Post Treatment (%)	
% INHIBITION IN COLLAGEN-6 HOURS POST	INH6_CO	% Inhibition of Collagen-induced Platelet Aggregation at 6 hours Post Treatment	Table 14.2.6.2.5 [325 mg dose] Table 14.2.6.2.6 [650 mg dose]
% INHIBITION IN COLLAGEN-24 HOURS POST	INH24_CO	% Inhibition of Collagen-induced Platelet Aggregation at 24 hours Post Treatment	Table 14.2.6.2.7 [325 mg dose] Table 14.2.6.2.8 [650 mg dose]

The revised Tables 14.2.6.1 to 14.2.6.4.2 (13 tables in total) are included in Attachment 1 with the correct variable names.

Secondly, the Agency requested the details of the method used to generate these data, which was submitted in the original NDA Serial 0000, Module 4, Section 4.2.1.2, Report PL2200-PHA-007 entitled "Effects of Modified Aspirin on Agonist-Induced Platelet Aggregation." A copy of this report is attached for convenience of the reviewer. Briefly, this method utilized platelet rich plasma obtained from study subjects at baseline and at 6-hour and 24-hour post treatment and measured percent platelet aggregation induced by arachidonic acid or type I fibrillar collagen. Measurement was performed by an optical platelet aggregometer. Analysis of the platelet aggregation was performed as the percent inhibition of platelet aggregation following treatment compared to baseline. Further details of the method as well as the results and interpretation are presented in the Report PL2200-PHA-007.

Warm regards,
Jason

Jason E. Moore, MS, MBA, RAC
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From: Adams-King, Janice [mailto:Janice.Adams-King@fda.hhs.gov]
Sent: Friday, October 19, 2012 1:54 PM
To: Jason Moore
Subject: Assay methods for NDA 203697 (ASA/PC)

Hi James, Can you please respond to the following information request as soon as possible. Also, can you please call me regarding your pending clinpharm submission, dated October 9, and the IND 74290 protocol. Thank you, Janice

Information Request:

"It is not clear to us what data are presented under section 14.2.6 and in the analysis dataset plateagg.xpt. Are these % platelet aggregation or as you have labeled it

arachidonic acid levels? Also, please provide details of the method used to generate these data".

CAPT Janice Adams-King, RN, BSN, MS (USPHS)
Regulatory Health Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV, CDER/FDA
10903 New Hampshire Avenue, Bldg. 22, Room 5408
Silver Spring, MD 20993
Phone: 301-796-3713 Fax: 301-796-9899
Janice.Adams-King@fda.hhs.gov

From: Peacock, Celia [mailto:Celia.Peacock@fda.hhs.gov]
Sent: Wednesday, July 25, 2012 9:56 AM
To: Jason Moore
Cc: Adams-King, Janice; Peacock, Celia
Subject: NDA 203697 IR July 25, 2012

Good Morning Jason. Below, please find an information request for NDA 203697. *Send this information by COB Aug 3, 2012.*

I am covering for Janice Adams-King until August 3, 2012, so please call me if you have any questions.

1. For the PK studies (PL-ASA-001 and PL-ASA-003) submit in separate SAS transport files (.xpt) with information including,

- the concentrations (including pre-dose concentration) of each analyte with information of treatment, dose, subject number, nominal time, actual time, sequence, period, etc. The dataset should allow the Agency to conduct non-compartmental analysis using WinNonlin directly without any transformation of the dataset.

- the non-compartmental analysis PK parameters of each analyte for each subject with information of treatment, dose, subject number, sequence, period, etc. The dataset should allow the Agency to conduct bioequivalence (BE) analysis using WinNonlin and SAS directly without any transformation of the dataset.

2. Submit complete annotated font specifications for the Drug Facts label for each outer container. You should refer to 21 CFR 201.66(d) format requirements to see what we need. Another reference would be Guidance for Industry - Labeling OTC Human Drug Products (Small Entity Compliance Guide).
For example, according to 201.66(d)(2), the Drug Facts title type size should be larger than the largest type size used in Drug Facts labeling. Subheadings, such as "Do not use" should be greater than or equal to 6 pt. It is difficult to determine whether these specifications are being met based on the submission.
We need the specifications for each format requirement listed in 201.66 for your labels [Drug Facts title, Drug Facts (continued) title, other headings, subheadings, text, bullets, leading, barlines, hairlines].

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
03/29/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203697 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Established/Proper Name: Aspirin 325 mg Dosage Form: capsule, liquid-filled		Applicant: PLx Pharma, Inc. Agent for Applicant (if applicable):
RPM: Janice Adams-King		Division: Nonprescription Clinical Evaluation

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

*

Provide a brief explanation of how this product is different from the listed drug.

*This application provides for change in dosage from, from tablet to liquid-filled capsule and does not conform to the Dissolution Testing specifications required in the TFM (53 Fed Reg at 46260, Subpart D-Testing Procedures) as defined in the USP monograph for Aspirin Capsules.

☐ This application does not reply upon a listed drug.
☒ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 1/14/2013

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions

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

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

• Proposed action • User Fee Goal Date is 1/14/2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☒ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

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

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

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 1/14/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	

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

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	1/10/2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Non-acceptable – 8/17/2012; Reviews: 8/17/2012
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA 11/27/12 ☐ DMPP/PLT (DRISK) ☐ ODPD (DDMAC) ☐ SEALD ☐ CSS ☐ Other reviews IDS – 1/14/13; 1/11/13; 1/2/13; 12/10/12
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	6/15/12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 12/7/12
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 12/26/12
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: PREA not triggered • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included – PMHS Consult Review

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

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	1/3/13; 11/1/12; 11/19/12; 7/25/12
❖ Internal memoranda, telecons, etc.	1/3/13; 12/20/12
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 12/16/11
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 9/23/10
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	6/17/11; 11/2/9; 9/7/7
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 1/14/13
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12/26/12
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	12/26/12
• Clinical review(s) *(indicate date for each review)*	12/10/12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	12/10/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DAAAP 12/11/12; DCRP 11/30/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 10/31/12
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/7/12; 11/14/12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None (See OSI – 10/31/12) 12/7/12
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/10/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None Botanical – 11/19/12; 5/17/12
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 1/8/13; 12/10/12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	12/10/12 – See CMC Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 1/8/13 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

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

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/

JANICE ADAMS
03/29/2013

MEMORANDUM

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

MEETING DATE: December 20, 2012
TIME: 12:30 PM
LOCATION: WO Bldg 22, Rm 4201

APPLICATION: NDA 203697

DRUG NAME: (b) (4) (Aspirin) Capsules, 325 mg

TYPE OF MEETING: Proprietary Name

APPLICANT: PLX Pharma Inc.

MEETING CHAIR: Todd Bridges, DMEPA Team Leader

MEETING RECORDER: Ermias Zerislassie, OSE Project Manager

FDA ATTENDEES: Alice Tu, PharmD, DMEPA Safety Evaluator
Todd Bridges, DMEPA Team Leader
Ermias Zerislassie, OSE Project Manager

APPLICANT ATTENDEES:

PLx Pharma:

- Jason E. Moore, MS, MBA, RAC, Vice President
- Ron Zimmerman, President & CEO
- Gary Mossman, COO
- Upendra Marathi, PhD, Senior Vice President
- Joy Coraza, MS, Regulatory & Quality Manager

(b) (4)

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

Previously, DMEPA reviewed the proposed name (b) (4) for this product. A teleconference with the Applicant was held on April 19, 2012 to discuss the proposed name (b) (4) DMEPA explained that the proposed name (b) (4) contains the (b) (4) in the name. Following the teleconference, the proprietary name request submission for (b) (4) was withdrawn by the Applicant on May 8, 2012.

(b) (4) was the second proposed proprietary name for this product, which was found unacceptable because the proposed name was misleading and was vulnerable to name confusion with the names (b) (4). The denial letter for the proposed name (b) (4) was sent to the Applicant on August 17, 2012.

(b) (4), submitted on December 6, 2012, is the third proposed proprietary name. Due to the approaching OND PDUFA of January 14, 2013, DMEPA decided to call the Applicant as a courtesy to notify them of our decision in advance of the denial letter.

Meeting Objectives:

DMEPA requested this teleconference to notify you of our safety concerns with the proposed proprietary name, (b) (4)

1. (b) (4)

   We note that the name (b) (4) was <u>not</u> identified in the (b) (4) proprietary name assessment.

2. [redacted] (b) (4)

We note that you did not submit an alternate name in your submission.

Now we would like to discuss your regulatory options.

Regulatory Options:

1. We recommend withdrawing your request for the proposed proprietary name, [redacted] (b) (4), and submit a new name for review.

OR

2. You may choose to wait for us to complete our review and issue a denial letter for the name. However, if you choose to wait for the denial letter, you won't be able to submit another name for review until after you have received the denial letter, which will be issued on or before the PDUFA date for your request for name review, March 10, 2013.

T-con Discussion

Applicant's consultant [redacted] (b) (4) stated that it seems proprietary names that are derived from "Aspirin" look like other aspirin product proprietary names marketed under the OTC Monograph. [redacted] (b) (4) also stated that a lot of these OTC Monograph aspirin products have names that appear to be derived from "Aspirin". They finally asked: Has there been any confusion between these names, and why would this proposed name pose any more risk than those names out there?

DMEPA responded that we didn't specifically perform a FAERS search for this name review. However, we are not aware of any name confusion medication errors between aspirin product marketed under the OTC Monograph because if we did identify error, then we'd contact the respective manufacturer. Additionally, we reviewed this proposed name like we do with any other proposed proprietary name for an application product, and so we would deny the proposed name because we don't want to introduce a name that presents medication error risk to the market place.

The Applicant acknowledged our safety concern, and asked for clarification on administrative processes of pursuing another name.

DMEPA clarified that the Applicant does not have to withdraw (b) (4) if they don't want to, and can certainly wait for our denial letter. However, in the meantime they won't be able to submit another proprietary name for review.

FDA explained the following to the Applicant:

1) An action can be taken on the application under the established name.
2) If they decide to withdraw the (b) (4) name and submit another name prior to the application action date, the proprietary name submitted prior to the action date would continue to be reviewed under the then existing OSE PDUFA clock.
3) If the product were to be approved under the established name, then the Applicant would need to submit a prior approval labeling supplement following the proprietary name approval to place the new name onto the container label and carton labeling.

DMEPA asked if the Applicant will wait until they have an acceptable proprietary name or if they will market under the established name if their product is approved. The Applicant stated they will wait for an acceptable proprietary name before marketing.

In conclusion, the Applicant stated that they plan to withdraw the submission for (b) (4), and will submit a new proprietary name review request either before or after the application action date.

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/s/

ERMIAS ZERISLASSIE
01/03/2013

CHI-MING TU
01/03/2013

TODD D BRIDGES
01/03/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 203697

PROPRIETARY NAME REQUEST
UNACCEPTABLE

PLx Pharma Inc.
8285 El Rio, Suite 130
Houston, TX 77054

Attention: Jason E. Moore, MS, MBA, RAC
Vice President

Dear Mr. Moore:

Please refer to your New Drug Application (NDA) dated March 12, 2012, and received March 14, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Aspirin Capsules, 325 mg.

We also refer to your May 17, 2012, correspondence, received May 21, 2012, requesting review of your proposed proprietary name, (b) (4) We have completed our review of the proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

1. (b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Daniel Reed at (301) 796-2220.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
08/17/2012

Peacock, Celia

To: jason.moore@plxpharma.com
Subject: NDA 203697 IR July 25, 2012

Good Morning Jason. Below, please find an information request for NDA 203697. *Send this information by COB Aug 3, 2012.*

I am covering for Janice Adams-King until August 3, 2012, so please call me if you have any questions.

1. For the PK studies (PL-ASA-001 and PL-ASA-003) submit in separate SAS transport files (.xpt) with information including,
   - the concentrations (including pre-dose concentration) of each analyte with information of treatment, dose, subject number, nominal time, actual time, sequence, period, etc. The dataset should allow the Agency to conduct non-compartmental analysis using WinNonlin directly without any transformation of the dataset.
   - the non-compartmental analysis PK parameters of each analyte for each subject with information of treatment, dose, subject number, sequence, period, etc. The dataset should allow the Agency to conduct bioequivalence (BE) analysis using WinNonlin and SAS directly without any transformation of the dataset.

2. Submit complete annotated font specifications for the Drug Facts label for each outer container. You should refer to 21 CFR 201.66(d) format requirements to see what we need. Another reference would be Guidance for Industry - Labeling OTC Human Drug Products (Small Entity Compliance Guide).

For example, according to 201.66(d)(2), the Drug Facts title type size should be larger than the largest type size used in Drug Facts labeling. Subheadings, such as "Do not use" should be greater than or equal to 6 pt. It is difficult to determine whether these specifications are being met based on the submission.

We need the specifications for each format requirement listed in 201.66 for your labels [Drug Facts title, Drug Facts (continued) title, other headings, subheadings, text, bullets, leading, barlines, hairlines].

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/s/

CELIA R PEACOCK
07/25/2012

MEMORANDUM

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

MEETING DATE: April 19, 2012
TIME: 1:00 pm – 1:30 pm
LOCATION: WO 22 Room 5266
APPLICATION: NDA 203697
DRUG NAME: Aspirin Capsules, 325 mg
TYPE OF MEETING: Proprietary name for product

APPLICANT: PLx Pharma, Inc.

MEETING CHAIR: Todd Bridges, Team Leader, DMEPA

MEETING RECORDER: Cherye Milburn, Safety Regulatory Project Manager

FDA ATTENDEES:

Todd Bridges, Team Leader, DMEPA
James Schlick, Safety Evaluator, DMEPA
Cherye Milburn, Project Manager, OSE
Darrell Jenkins, Team Leader, Office of Surveillance and Epidemiology

EXTERNAL CONSTITUENT ATTENDEES:

Jason E. Moore, MS, MBA, RAC, Vice President, PLx Pharma Inc.
Joy M. Coraza, MS, Regulatory and Quality Manager, PLx Pharma Inc.
(b) (4)

Background:

DMEPA requested this teleconference to inform the Applicant of our concerns regarding their proposed proprietary name, (b) (4) for this product.

Discussion:

FDA's Findings:

As stated in FDA' concept paper titled, *PDUFA Pilot Project – Proprietary Name Review* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072229.pdf), FDA screens proposed proprietary names for naming characteristics known to cause or contribute to medication errors. (b) (4)

[redacted] (b) (4)

FDA finds your proposed name unacceptable. (b) (4)

We would like to discuss the regulatory options.

Choice #1: You may withdraw your proposed name and submit an alternate proprietary name.

OR

Choice #2: You may wait for us to issue a denial letter regarding the proposed proprietary name.

Questions:

No Questions

Conclusion:

After discussion with the sponsor, PLx stated they would let us know early next week which choice they would go with.

On April 25, 2012, received a phone call from Jason Moore of PLx Pharma and he stated we would receive a withdrawal letter for the name the first of next week. They will send a request for a new name in a few weeks.

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/s/

ERMIAS ZERISLASSIE
05/14/2012

TODD D BRIDGES
05/14/2012

Department of Health and Human Services | Public Health Service
Food and Drug Administration
Rockville, MD 20857

JAN 20 2012

Jason E. Moore
Vice President
PLx Pharma Inc.
8285 El Rio Street, Suite 130
Houston, TX 77054

RE: PLx Pharma Inc., Small Business Waiver Request # 2012.017 for New Drug Application 203697 for PL2200 Aspirin Capsules

Dear Mr. Moore:

This responds to your November 3, 2011, letter requesting a waiver of an application user fee under the small business waiver provision, section 736(d)(1)(D)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2012.017). You request a waiver of the fiscal year (FY) 2012[2] human drug application fee for new drug application (NDA) 203697 for PL2200 Aspirin Capsules. For the reasons described below, the Food and Drug Administration (FDA) grants the PLx Pharma Inc. (PLx) request for a small business waiver of the application fee for NDA 203697 for PL2200 Aspirin Capsules.

According to your waiver request:

- (b) (4)
- The NDA 203697 for PL2200 Aspirin Capsules is the company's first human drug application.

PLx expects to submit its NDA 203697 to the Agency on or around January 31, 2012.

Under section 736(d)(1)(D) of the Act, a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate[3] submits to the FDA for review. As outlined in section 736(d)(4) of the Act,[4] a small business is entitled to a waiver when the business meets the following criteria:

(1) The business must employ fewer than 500 persons, including employees of its affiliates.
(2) The business does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce.

[1] 21 U.S.C. 379h(d)(1)(D).
[2] FY 2012 = October 1, 2011, through September 30, 2012.
[3] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(11)).
[4] 21 U.S.C. 379h(d)(4).

(3) The marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA has reviewed its records, the Small Business Administration (SBA) size determination dated December 7, 2011,[5] and the information you submitted. Considering all the relevant factors, FDA concludes that PLx meets the statutory requirements of the Act. Consequently, your request for a small business waiver of the application fee for NDA 203697 is granted, provided the marketing application is submitted before November 7, 2012, 1 year after the base date for the size determination. We have notified the FDA Office of Financial Management (OFM) of this waiver decision.

FDA records show that PLx has not yet submitted the full NDA 203697. **Please include a copy of this letter granting your waiver with your submission of NDA 203697.** Once submitted, if FDA refuses to file the application or if PLx withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, PLx should contact this office at least 90 days before it expects to resubmit its marketing application to determine whether PLx continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-796-3602.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

[5] The SBA confirmed on December 7, 2011, that PLx is a small business with the following affiliates: PLx Pharma Inc., and PLx Pharma Ireland Ltd.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

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

Please mark the applicable checkbox.

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

Clinical Investigators		
	See attached addendum.	

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

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

NAME	TITLE
Jason E Moore, MS, MBA, RAC	Vice President
FIRM/ORGANIZATION PLx Pharma Inc.	
SIGNATURE Jason Moore	DATE *(mm/dd/yyyy)* 12/27/2011

Paperwork Reduction Act Statement

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

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

FORM FDA 3454 (10/09)

PSC Graphics (301) 443-1090 EF

FINANCIAL CERTIFICATION DISCLOSURE: ADDENDUM TO FORM 3454

Following is a list of those clinical investigators covered by Form 3454, for PLx Pharma Inc. NDA 203697.

Name	Address	Phone Number
Byron Cryer, MD	Dallas VA Medical Center 4500 S Lancaster Rd, Room 5B139 Dallas, TX 75216-7167	Phone: 214-374-3500
Alan Kivitz, MD	Altoona Center for Clinical Research 1125 Old Rte 220 N PO Box 909 Duncansville, PA 16635	Phone: 814-693-0300
Frank Lanza, MD	The Houston Institute for Clinical Research 7777 SW Freeway, Suite 720 Houston, TX 77074	Phone: 713-977-9095
Philip Miner, Jr, MD	Oklahoma Foundation for Digestive Research 1000 N Lincoln Blvd, Suite 210 Oklahoma City, OK 73104	Phone: 405-271-4644
Howard Schwartz, MD	Miami Research Associates 6141 Sunset Drive, Suite 301 Miami, FL 33143	Phone: 305-598-3125 ext 4258
Michael Schwartz, DO	Jupiter Research Associates 1002 S Old Dixie Hwy, Suite 301 Jupiter, FL 33458	Phone: 561-743-4160

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074290

MEETING MINUTES

PLx Pharma Inc.
Attention: Jason E. Moore, MS, MBA, RAC
Vice President
8285 El Rio, Suite 130
Houston, TX 77054

Dear Mr. Moore:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PL 2200 (aspirin) capsules, 325 mg.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on December 16, 2011. The purpose of the meeting was to discuss the content of a future NDA submission.

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

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

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	December 16, 2011
Meeting Location:	FDA/White Oak 10903 New Hampshire Avenue Building 22, Room 1415 Silver Spring, MD 20903
Application Number:	IND 74290
Product Name:	PL 2200 (aspirin) capsules, 325 mg
Indication:	Pain Reliever, fever reducer
Sponsor/Applicant Name:	PLx Pharma, Inc.
Meeting Chair:	Joel Schiffenbauer, M.D.
Meeting Recorder:	LT James Lee, Pharm.D.

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation:
Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Medical Team Leader
Priscilla Callahan-Lyon, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacologist/ Toxicologist
James Lee, PharmD., Regulatory Project Manager

Office of Drug Evaluation IV
Shaw Chen, M.D., Deputy Director
Jinhui Dou, Ph.D., Pharmacologist

Division of Nonprescription Regulation Development
Elaine Abraham, Pharm.D., Interdisciplinary Scientist

Division of Clinical Pharmacology II
Yun Xu, Ph.D., Clinical Pharmacology Team Leader
Suresh Naraharisetti, Ph.D., Clinical Pharmacology Reviewer

Division of New Drug Quality Assessment III
Ali Al Hakim, Ph.D., Chemistry Branch Chief
Sheldon Markofsky, Ph.D., Chemistry Reviewer
Swapan De, Ph.D., CMC Lead
John Duan, Ph.D., Biopharmaceutical Reviewer

SPONSOR ATTENDEES
PLx Pharma, Inc.
Upendra Marathi, PhD, MBA, Senior Vice President
Jason Moore, MS, MBA, RAC, Vice President
Shaun Gammill, Director of Manufacturing Operations
(b) (4)
(b) (4)
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(b) (4)

1.0 BACKGROUND

PLx Pharma, Inc. (PLx) submitted a meeting request on September 16, 2011 to discuss the level of characterization and components of (b) (4), acceptability of the proposed dissolution methods, drug product release specifications (b) (4), concurrence on the acceptability of the development plan for the safety and efficacy of the proposed aspirin capsules, and to discuss regulatory requirements for an NDA submission. A type B meeting was granted and scheduled for December 16, 2011. The FDA's preliminary responses to the questions enclosed in the November 9, 2011 meeting briefing package were provided to PLx via electronic mail on December 14, 2011. These preliminary responses appear in italics below.

Following introductions, the meeting agenda consisted of further discussion regarding questions 2, 3, 7 and comments regarding biopharmaceutics.

2. DISCUSSION

Lecithin Questions

Question 1:

Approximately (b) (4) of the composition of the soy lecithin excipient used in PL2200 (b) (4) has been characterized and accounted for analytically. Given that this lecithin is a botanically derived inactive ingredient/excipient, (b) (4) does the Agency agree that this degree of lecithin characterization is sufficient?

FDA Preliminary Response:

We do not agree with your statement that the degree of characterization of soy lecithin, as described in the meeting package, (b) (4)

We do agree, however, that the soy lecithin (b) (4) characterization is sufficient as a botanically derived excipient, provided that the soy lecithin batches will also be tested and have permissible levels of contaminants (e.g., microbial, heavy metals, pesticides). See FDA responses for Q2.

Question 2:

As (b) (4) will be manufactured according to current Good Manufacturing Practices (with a DMR to be filed for concurrent review with the PL2200 NDA), PLx believes that the specifications described herein for this lecithin product are sufficient. Does the Agency agree?

FDA Preliminary Response:

We have concerns about your proposed specifications for (b) (4). While (b) (4) and your degree of characterization of this product may be suitable as an excipient for some drug products, we cannot determine whether your specifications for (b) (4) or for the

substances of this lecithin-based mixture in your drug product are adequate for your proposed aspirin capsules for the following reasons:

- *You have not demonstrated that the upper and lower limits of your proposed specifications for the significant components or other variables in (b) (4) will afford satisfactory and consistent dissolution profiles and quality attributes for your drug product. The analyses of the batches of (b) (4) that you have employed for your drug product, as summarized in Table 39 and in the certificate of analysis of your lecithin-based excipient, show (b) (4) ranges for the components in (b) (4) than they are in your proposed specifications. Moreover, there is no lower limit for the (b) (4) specification. Accordingly, you should (b) (4) the ranges of the acceptance criteria for these components and other relevant variables or justify the (b) (4) limits that you propose.*

- *Since an adequate (b) (4) specification should be based on a satisfactory and discriminating dissolution method, you should address our dissolution comments from our 9/23/2010 meeting, as well as in our attached **Additional Biopharmaceutics Comments (see below).***
- *Since it is not yet clear if the levels of the various components in (b) (4) can affect quality attributes of the drug product at release and through its expiry and whether or not these levels change on storage of the drug product, we suggest that HPLC profiles of the (b) (4) and their related possible degradants in the capsules be monitored, by a validated analytical method, in your stability program under the long term and accelerated storage condition.*

- *In addition, since (b) (4) is sensitive to storage conditions, acceptance of this excipient should require a manufacturer's COA and appropriate in-house acceptance testing.*

Discussion:

- PLx stated their agreement with the Agency's concerns regarding non-ideal storage, shipping, and environmental situations and its effects on (b) (4)

- PLx agreed to provide upper and lower limits of the proposed acceptance specifications for the significant components and other variables in (b) (4)

- PLx also stated their understanding of FDA's preliminary response to Question 2 and will submit primary data package, based on phosphorous NMR, for PC and (b) (4) that will show a change in drug product over time.

- FDA repeated the request that, in addition to PC and (b) (4) by phosphorous NMR, the levels of the various components and their degradants in (b) (4) as measured by an HPLC profile of this excipient in the drug product, should be monitored in the stability program under long term and accelerated storage conditions.

- It was agreed that PLx will justify their specification and stability protocol in their NDA submission. FDA noted that acceptance of the specifications and stability protocol will be a review issue.

- FDA indicated that since the aspirin in their proposed drug product was manufactured as (b) (4), ICH requires a particle size distribution specification for this drug substance. PLx stated that a particle size distribution will be part of the aspirin drug substance specification.

Question 3:
As (b) (4) is a cGMP-quality excipient that (b) (4) (b) (4) Does the Agency agree with this plan?

FDA Preliminary Response:
We do not agree for reasons explained in our response to Question 2. (b) (4) *Therefore PC, (b) (4), and their degradants should be monitored in your stability program by a validated analytical method.*

Discussion:

- With respect to the dissolution specification and procedure, PLx stated that the lipids in (b) (4) (b) (4) but the resulting products are within acceptable levels for a drug product. PLx stated that the reason for (b) (4) PLx will provide complete datasets with two different paddle speeds (150 RPM (b) (4) for comparison of the resulting products.

- (b) (4)

- FDA emphasized that the rotation speed (b) (4). However, if an IVIVC can be confirmed after review, FDA would take it into consideration for the evaluation of the dissolution method. FDA recommended submitting the IVIVC report with sufficient supporting data for review and feedback.

PL2200 Proposed Label Question
Question 4:
The PL2200 proposed label for product marketing as a nonprescription product for temporary relief of minor aches and pains due to headaches, muscular aches, arthritis, toothache, backache, the common cold, and menstrual cramps, and for temporary reduction in fever is provided in Appendix 1. The proposed label conforms, in general, with the Drug Facts style as per the Agency's requirements for marketed aspirin tablets. Does the Division agree that the proposed label would be the required label for PL2200?

FDA Preliminary Response:
We agree that the proposed draft labeling appears to conform, in general, with the Drug Facts requirements; however, it is premature to agree that the proposed label would be the required label for PL2200. Final labeling will be part of the NDA review and will be based on the data provided.

We remind you to submit annotated specifications of your Drug Facts label for each stock keeping unit that you propose to market under your NDA.

Clinical Questions
Question 5.
Approach to ISE. Because PLx has not conducted any new studies on the efficacy of aspirin as an analgesic or antipyretic, as the PL2200 NDA will be submitted pursuant to §505(b)(2) of the Federal Food, Drug and Cosmetic Act and consistent with the uses outlined in the Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use Tentative Final Monograph (IAAA TFM), PLx proposes the following approach for the Integrated Summary of Efficacy in the NDA. PLx will conduct a search of the worldwide literature for reports of adequate and well-controlled studies of the efficacy of aspirin. The search will focus on those clinical uses identified in the IAAA TFM (i.e., temporary relief of minor aches and pains due to headaches, muscular aches, arthritis, toothache, backache, the common cold, and menstrual cramps, and for temporary reduction in fever). To the extent possible, PLx will provide an analysis of the aspirin efficacy literature, with a specific focus on dose response, consistency of findings across studies, time to demonstrable effect and duration of response. A tabulation of relevant efficacy data will also be provided. Does the Agency agree with this approach?

FDA Preliminary Response:
This is acceptable. You should provide all reference articles, translated into English as necessary.

Question 6:
Approach to ISS. The safety of PL2200 has been evaluated in two pharmacokinetic studies (PL-ASA-001, PL-ASA-003) and one gastrointestinal safety and tolerability study (PL-ASA-002). For the Integrated Summary of Safety, PLx plans to provide an analysis of

overall extent of exposure, exposure by dose, and a comparison of demographic and other characteristics of the study populations. Because of the significant differences in study design between the studies, as well as the minimal adverse events in two of the three studies (]AE in PL-ASA-001 and 0 AEs in PL-ASA-003), the detailed analysis of adverse events (e.g., system/organ class, severity of symptoms), will be limited to PL-ASA-002. Additionally, PLx proposes to conduct a search of the FDA Adverse Event Reporting System (AERS) data for current safety reports with suspect mentions of single ingredient aspirin products (i.e., products containing acetylsalicylic acid only). The search will be limited to reports with an initial FDA receive date from January 1, 2001 to December 31, 2010 to provide adverse events from a safety update period approximately since the time that the NDA for the most recent aspirin product (Extra Strength Bayer® Plus Aspirin) was submitted to the Agency. Query results will be further limited to reports where the suspect aspirin product was believed to have been an oral formulation. Finally, a summary of information on the safety of aspirin from the published literature will be provided. Does the Agency concur with this approach?

FDA Preliminary Response:
This is acceptable. You should provide all reference articles, translated into English as necessary.

Question 7:
PLx believes that the clinical pharmacology of aspirin is well established and is fully described in 21 CFR 343.80, consistent with nonprescription indications. Therefore, PLx does not intend to provide additional clinical pharmacology information other than the bioavailability results of studies PL-ASA -001 and PL-ASA-003. Does the Division agree that no additional clinical pharmacology information will be required?

FDA Preliminary Response:

- *You conducted a single dose fasted bioequivalence study comparing your product with Genuine Bayer® Aspirin tablets at both 325 mg dose (1 x 325 mg) and 650 mg dose (2 x 325 mg). You also conducted a food effect study for your product at 650 mg dose (2 x 325 mg). These studies will be adequate to support the NDA filing of your product from a clinical pharmacology perspective. Whether the study results will be sufficient to support approval of your NDA will be a review issue.*

- *The final to-be-marketed product should be used in the clinical pharmacology studies. If not, you need to provide adequate bridging information or justification as to why the study results can be used to support your final to-be-marketed product.*

- *In the BE study PL-ASA-001, your product met the BE criteria with the reference product, Genuine Bayer® Aspirin tablets at the 650 mg dose. However, it did not meet the BE criteria at the 325 mg dose. As advised during the EOP2 meeting, you should provide adequate rationale for the lack of bioequivalence at the 325 mg dose when the*

same product showed bioequivalence at the 650 mg dose. You will also need to provide a rationale for why this difference is not of clinical concern.

- *You did not mention the type of meal used in the synopsis of your food effect study, PL-ASA-003. Usually we recommended a high-calorie, high-fat meal during a food-effect study. A preliminary review of the synopsis submitted on Dec 6, 2011 indicates that there is 22% lower Cmax and 11% lower AUC for your product with food in comparison to the fasted state. Although the geometric mean ratio for AUC between fasted and fed conditions met the BE criteria of 80 to 125% range, it fell out of the range for Cmax. Therefore, you need to provide adequate justification in your NDA submission to demonstrate that the observed food effect with your product will not have clinical significance.*

Discussion:
PLx stated their understanding of the FDA's preliminary response and will address all concerns in the NDA submission. Regarding the FDA's concerns with a food-effect, PLx plans to submit data showing any food effect is not clinically significant. FDA asked PLx to provide data in the NDA submission to show that the observed food effect with PL2200 is not different from the currently approved aspirin immediate release products (e.g. the reference product that PLx is relying on).

FDA requested clarification regarding the tested product and the final to-be-marketed product. PLx responded that the planned marketing product will have the addition of printing on the surface of the tablet; all other components are identical. FDA reminded PLx that a biowaiver request must be submitted if PLx believes that the differences between the tested product and the final to-be-marketed product are minimal and no bridging studies are necessary. PLx stated their understanding.

Clinical Data Submission Questions
Question 8.
PLx proposes that all data collected during each of the studies to be included in the NDA submission will be submitted as Version 5 SAS transport files. For each study: Annotated case report forms will be provided to show how data that were collected directly from the case report forms were mapped to each dataset. Datasets imported from laboratory (including PK) vendors will also be provided, along with any dataset specifications that were provided by the external vendor. Analysis datasets created for the purposes of PK or efficacy analyses will also be included, and a dataset specification will be provided for each analysis dataset. The dataset specification will detail how each variable was created. The analysis dataset for PL-ASA-002 will also be included. Is this plan acceptable?

FDA Preliminary Response:
Yes, the plan is acceptable.

Question 9.
As described above, the three completed clinical trials of PL2200 were all performed in healthy volunteers, without efficacy endpoints, utilizing pharmacokinetic and pharmacodynamic endpoints, and no SAEs, discontinuations due to adverse events, or deaths, and only minimal adverse events, were observed in these studies. Accordingly, use of individual patient case report tabulations would have limited value for the reviewers in this clinical program. Therefore, PLx does not plan to submit clinical data (case report) tabulations (CRTs) for all subjects enrolled in trials PL-ASA-001, PL-ASA- 002, and PL-ASA-003. Is this plan acceptable?

FDA Preliminary Response:
Yes, the plan is acceptable.

Question 10.
In the PL2200 clinical program, which consists of 3 clinical trials, there were no Serious Adverse Events (SAEs), discontinuations due to adverse events, or deaths that occurred. Consequently, submission of completed subject Case Report Forms is not planned. Is this plan acceptable?

FDA Preliminary Response:
Yes, the plan is acceptable.

Nonclinical Pharmacology/Toxicology Question
Question 11.
PLx believes that the safety and efficacy of aspirin in humans is well established, as will be summarized in Module 2 of the PL2200 CTD new drug application. Nonetheless, PLx proposes to provide a review of the literature with respect to the nonclinical safety of aspirin. PLx anticipates identifying studies in the literature that will allow a review of the toxicology of aspirin, and will provide a review and synthesis of this information, together with the articles referenced therein and used to reach nonclinical safety conclusions. Is this plan acceptable?

FDA Preliminary Response:
Yes, your plan to address the nonclinical safety of aspirin appears acceptable.

NDA Administrative/Procedural Questions
Question 12.
PLx will submit its New Drug Application as an electronic Common Technical Document (eCTD) via the Electronic Submissions Gateway. The eCTD will be prepared by (b) (4) (b) (4) (b) (4) (b) (4) **will publish the eCTD in accordance with relevant guidance for the publishing and validation of an eCTD submission for FDA review.** (b) (4) **has received prior and recent approval of eCTD submissions following a standardized process to be used or the upcoming PL2200**

submission. Based upon the successful filing of eCTDs by [redacted], we do not believe a PLx-specific eCTD Pilot Submission will be necessary prior to the PL2200 NDA submission. Does the Agency agree?

FDA Preliminary Response:
We agree that a Pilot Submission is not necessary.

Question 13.
Does FDA anticipate requesting PLx to participate in an Applicant Orientation Presentation?

FDA Preliminary Response:
No, at this time we do not anticipate an Applicant Orientation Presentation.

Additional Biopharmaceutics Comments:

Dissolution Test:
We would like to remind you that the dissolution method report supporting the selection of the proposed test should be included in your NDA submission. This report should include the following information:

1. *Solubility data for the drug substance covering the pH range.*
2. *Detailed description of the dissolution method proposed for your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed (50, 75, 100 rpm, etc), pH, assay, sink conditions, etc.) used to select/identify the proposed dissolution method as the most appropriate. The testing conditions used for each test should be clearly specified.*
3. *The complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).*
4. *Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).*

If the above information is available during the IND, please provide the dissolution method report for review.

Dissolution Acceptance Criterion:
In your meeting document you are proposing an acceptance criterion of Q= [redacted] for the dissolution test. However, the provided dissolution data indicate that a [redacted] criterion can be set for your product (i.e., Q= [redacted] at 30 minutes). Therefore, we recommend that you collect complete dissolution profile data from the bio-batches (PK and clinical) and primary (registration) stability batches of your product. These data should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and

specification value). For the setting of the drug dissolution acceptance criterion, the following points should be considered:

- *The dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.*
- *The specification-time point should be set when Q =* (b) (4) *of dissolution occurs.*

In-Vitro In-Vivo Correlation

You reported in the meeting document that you developed a "Level A" IVIVC. If you want to pursue your proposed IVIVC model, you would need to demonstrate its robustness by performing validation (internal and external predictability) (refer to IVIVC guidance for detail information about general considerations and development and validation of a Level A IVIVC).

Discussion:

FDA suggested that PLx provide AUC in addition to the planned IVIVC for validation. AUC is a requirement for the assessment of the rate and extent of absorption. (b) (4)

FDA asked for the scaling factor. PLx responded that their scaling factor is (b) (4) FDA recommended that PLx submit their data prior to NDA submission to determine if IVIVC is acceptable.

Additional Division of Medical Error Prevention and Analysis Comments

1. *Ensure that a unique code imprint is present on the proposed PL2200 capsule per 21 CFR 206.10.*
2. *Ensure the text is legible with adequate contrast when printed on the blister of the proposed 8-count cold form blister.*

Additional Administrative Comments

Comments shared with you today are based upon the contents of the meeting package, which is considered to be an informational aid to facilitate the meeting discussion.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients 0 to < 17 years old unless this requirement is waived, deferred, or inapplicable. In addition, PREA requires that the FDA

Pediatric Review Committee (PeRC) review all pediatric assessments, pediatric plans, and waiver or deferral requests prior to the Division taking an approval action.

We encourage you to submit a pediatric assessment with your NDA (a pediatric assessment is data sufficient to support dosing, safety, and efficacy in the relevant pediatric populations). However, if the pediatric assessment is not complete at the time of NDA submission, you must provide a pediatric development plan with a request for a waiver and/or deferral of studies in the appropriate pediatric populations, justification for waiving and/or deferring the assessments, and evidence that the deferred pediatric studies are being conducted or will be conducted with due diligence. In addition, provide a timeline for completion of deferred studies. At a minimum, you should provide the date the protocol will be submitted, the date the studies will be completed, and the date the studies will be submitted. We refer you to the industry guidance titled "How to Comply with the Pediatric Research Equity Act"(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf).

Under PREA, you may be required to conduct PK, safety and possibly efficacy studies for your proposed indication in pediatric patients < 17 years old pending FDA's decision on the need for data in this population. Please note that pediatric participants in clinical studies must be symptomatic or at risk for the condition(s) treated by the product to be consistent with 21 CFR 50 subpart D and the related ethical framework for research in children.

It appears that you intend to submit a 505(b)(2) application for your proposed product. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf).

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

You should be clear in your original submission when citing reliance on a listed drug and/or literature. Your submission should indicate the source, what the cited reliance is being used to support, and the scientific justification.

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf). Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

3.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS

1. PLx will submit primary data package for PC and (b) (4) to assess change in drug product over time; FDA repeated the request that, in addition to PC and (b) (4) assessed by phosphorous NMR, the levels of the various components and their degradants in (b) (4) as measured by an HPLC profile of this excipient in the drug product, should be monitored in the stability program under long term and accelerated storage conditions. PLx will need to show that the product functions appropriately with these stability characteristics.
2. PLx will provide a report of the dissolution method including paddle speeds along with justification in the NDA submission.
3. PLx understands that (b) (4) paddle speeds may be acceptable to the Agency provided that IVIVC and AUC data is also acceptable.
4. PLx will provide particle size distribution of aspirin in the NDA submission.
5. PLx will submit bioequivalence differences in the fed and fasted state to show that food effect is not clinically significant. PLx will need to provide a rationale for why BE criteria were not met for the 325 mg dose and provide a rationale for why this difference is not of clinical concern.
6. PLx will submit information regarding differences between the study drug and the final to-be-marketed drug product.
7. PLx will submit IVIVC data prior to submission of the NDA.

4.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for this meeting.

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

/s/

JOEL SCHIFFENBAUER
01/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074290

MEETING MINUTES

PLx Pharma Inc
Attention: Jason E. Moore, M.S., M.B.A., R.A.C.
Vice President
8285 El Rio, Suite 130
Houston, TX 77054

Dear Mr. Moore:

Please refer to your Investigational New Drug Application (IND) file for PL 2200 (aspirin) capsules, 325 mg.

We also refer to the meeting between representatives of your firm and the FDA on June 17, 2011. The purpose of the meeting was to discuss your proposed nonclinical safety data package in support of (b)(4), a proposed inactive ingredient for PL2200.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	IND
Meeting Date and Time:	June 17, 2011, 8:30 AM to 9:30 AM EST
Meeting Location:	FDA/White Oak 10903 New Hampshire Avenue Building 22, Room 1419 Silver Spring, MD 20903
Application Number:	IND 074290
Product Name:	PL 2200 (aspirin) capsule, 325 mg
Indication:	Pain Reliever/ Fever Reducer
Sponsor/Applicant Name:	PLx Pharma Inc.
Meeting Chair:	Andrea Leonard-Segal, M.D., M.S.
Meeting Recorder:	LT James Lee, Pharm.D.

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation (DNCE)
Andrea Leonard-Segal, MD, MS, Division Director
Joel Schiffenbauer, MD, Deputy Director
Daiva Shetty, MD, Medical Team Leader
Priscilla Callahan-Lyon, MD, Clinical Reviewer
Cindy Li, PhD, Pharmacology/ Toxicology Reviewer
Melissa Furness, Chief, Project Management Staff
James Lee, PharmD. Regulatory Project Manager

Office of New Drug Quality Assessment (ONDQA)
Ali Al-Hakim, PhD, Branch Chief

SPONSOR ATTENDEES

PLx Pharma Inc.
Upendra Marathi, PhD, MBA, Senior Vice President
Jason Moore, MS, MBA, RAC, Vice President

[redacted]
Estela Von Chong, Intern

1.0 BACKGROUND

PLx Pharma Inc. (PLx) submitted a meeting request to FDA on January 15, 2011, to discuss the proposed nonclinical safety data package in support of [redacted], a proposed inactive ingredient for PL2200. PLx is developing PL2200, a lipidic suspension of aspirin, for marketing as a pain reliever and fever reducer. The type B meeting was held on June 17, 2011.

Preliminary responses to the questions enclosed in the May 19, 2011 meeting briefing package were provided to PLx via electronic mail on June 16, 2011. These preliminary responses appear in italics below.

Following introductions, the meeting agenda consisted of further discussion of the following topics:

- Proposed package of nonclinical data in support of a NDA , including literatures studies and a 28-day nonclinical toxicity study
- Pharmacodynamic non-interference of [redacted]
- Chemistry comments regarding the addition of drug product acceptance criteria for each lipid component

2. DISCUSSION

Question 1.

The Position of PLx on the Conduct of Additional Nonclinical Toxicity Studies with [redacted]

[redacted] is a soy-based lecithin used as an excipient (325 mg/capsule) in the PLx aspirin product identified as PL2200. If a 60 kg individual took 12 capsules of PL2200 in a 24 hour period, he/she would receive a total daily dose of [redacted] or, for a 60 kg individual, [redacted] mg/kg/day of [redacted]

A comprehensive literature review (Appendix 3) completed by PLx on the toxicity of lecithins has shown that lecithins at high doses are well tolerated in nonclinical repeat-dose toxicity studies. Soybean – derived lecithins have been evaluated in rats in chronic studies of 13, 24, or 48 weeks in duration and in a 2 year carcinogenicity study. In dogs studies were up to 52 weeks in duration. The NOEL doses in rats varied by study but ranged from 1520 to 3000 mg/kg/day. The NOEL in the carcinogenicity study was 1470 mg/kg/day with no evidence of carcinogenic potential. The NOEL in the dog in the 52 week study was >750 mg/kg/day. The chronic and carcinogenicity studies conducted with soy-derived lecithins had NOEL doses that varied from [redacted] (dog) to [redacted] (rat) the dose of soy-derived lecithin a 60 kg individual would receive if

he/she took 12 PL2200 aspirin capsules, each containing (b) (4) of (b) (4) during one day.

The literature review further revealed that lecithins are not genotoxic or teratogenic.

In a 28-day oral gavage toxicity study in rats conducted by PLx, (b) (4), also a soy-based lecithin, was similarly well tolerated at daily doses of up to 2500 mg/kg/day. Based upon an assessment of the data by PLx, the NOAEL was 500 mg/kg/day or (b) (4) the dose of soy-derived lecithin a 60 kg individual would receive if he/she took 12 PL2200 aspirin capsules, each containing (b) (4) of (b) (4) during one day.

The target tissue was the nonglandular gastric mucosa, a structure not present in the human stomach.

The accumulated literature shows that soybean derived lecithins are well tolerated by rats and dogs at high doses. A similar observation was demonstrated in rats administered (b) (4) also a soy-derived lecithin. Based on these findings, PLx has come to the conclusion that additional studies that will use and sacrifice more laboratory animals to confirm the reported lack of chronic toxicity, reproductive toxicity, genotoxicity or carcinogenicity of a soy-derived lecithin like (b) (4) is not justifiable. The literature based safety assessment with the supplemental toxicity data support the use of (b) (4) as an excipient in the development of PL2200 and its market registration.

Based upon the information summarized in this document, does the agency have a concern with this position?

FDA Preliminary Response:

Your proposal to address the nonclinical safety concerns of (b) (4) through a literature based risk assessment with the supplemental toxicity data appears acceptable. The genetic toxicity studies do not appear necessary provided there are no novel components present in (b) (4). The adequacy, relevancy and quality of the nonclinical information to support the safety of your product will be a review issue and will be determined after review of all data in the submission.

Please refer to the International Conference of Harmonization (ICH) M3(R2) Guidance document titled "Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" which is available on the CDER webpage at the following location:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf.

The recommended strategies to support the safety evaluation of pharmaceutical excipients in drug products can be found in the FDA guidance titled "Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" at the following location

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129173.pdf. If you intend to rely on nonclinical information in the literature, you should submit complete copies of the relevant literature references, as well as a review and summary of the literature, for Agency's assessment.

We also have this chemistry comment for you. Although you have provided release data for (b) (4) from four batches, it is not clear whether ranges of (b) (4) are controlled during manufacture of (b) (4) Thus, acceptance criterion for each (b) (4) in (b) (4) needs to be proposed to assure reproducible synthesis and to limit lot to lot variation of (b) (4).

Additional Discussion:

PLx began the discussion by stating their understanding that FDA would find literature reviews and the 28-day toxicity study in rats to be sufficient for a NDA submission. The sufficiency of the data submitted, however, would be a review issue. FDA confirmed this comment.

PLx stated that they disagree with the CRO's estimated NOEL dose based on toxicity noted in the test animals due to difficulties with gavage, after the initial 28-day GLP toxicity study. PLx believes several factors may have made it difficult to interpret the data from the original study. These factors included: protocol changes, animal deaths, changes in dosing procedures, and changes in the procedures for handling test solution. (b) (4) making it difficult to conduct the gavage which resulted in toxicity noted in the test animals. However, PLx noted that after (b) (4), a subsequent 28-day non-GLP study was conducted and presented no dosing problems or animal deaths. PLx now plans to conduct a new GLP study incorporating the revised procedures to provide for more interpretable data. FDA agreed with this plan and requested that PLx submit the new study protocol for review.

FDA asked PLx to explain how they arrived at the dose used in the 28-day GLP study. PLx stated that the dose was simply the maximum feasible dose that was able to be delivered to the test animals (b) (4). (b) (4) In addition, the chosen maximum dose was already (b) (4)-fold multiple of the highest human daily dose based on mg/kg body weight.

FDA inquired as to the purpose and consequences of (b) (4) Specifically, the Agency was interested (b) (4) PLx responded that (b) (4) PLx also noted that (b) (4) is a very stable compound and data shows that (b) (4) does not have a significant effect on (b) (4) PLx agreed to provide data comparing stability of (b) (4) before and after (b) (4) as a part of the 28-day GLP study.

PLx acknowledged the preliminary chemistry comments and asked if FDA was open to having a teleconference to further discuss the acceptance criteria for reproducible continuous production of (b) (4) and to limit production variation. FDA responded that they are open to such a meeting and suggested that PLx submit a formal meeting request to ensure that the guidance provided will be officially recorded as meeting minutes.

FDA inquired regarding the variability of (b) (4) in the four lots presented in the meeting briefing package. More specifically, FDA commented that although the analytical characterization of (b) (4) appeared to be (b) (4) they would prefer to know 100% of the components of (b) (4) in order to know whether the unknown components could prove to be hazardous. PLx acknowledged FDA's concerns regarding the unknown components; however, PLx considers any component less than (b) (4) to be a trace component and proposed to provide in process controls and release criteria for the main mass only. PLx stated (b) (4) is a natural, soybean-derived product and that complete 100% characterization of all components for a botanical, (b) (4) product would not be realistic. In addition, PLx stated that they have relied on the *Guidance for Industry: Botanical Drug Products* and FDA's prior applications for guidance regarding the level of characterization for botanically derived ingredients. (b) (4) will be produced according to the current GMP standards for pharmaceutical excipients and PLx intends to submit a Type IV DMF prior to the NDA submission.

(b) (4)

Additional Administrative Comments:

It appears that you intend to submit a 505(b)(2) application for your proposed product. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs or as articulated in an OTC Drug Monograph, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" between your proposed drug product and

each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

You should be clear in your original submission when citing reliance on a listed drug and/or literature. Your submission should indicate the source, what the cited reliance is being used to support, and the scientific justification.

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

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf). Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

Depending on your development program, we encourage you to request and attend, at a minimum, a pre-NDA meeting prior to submitting a new drug application to discuss the content and format of your application.

Additional Discussion:

PLx stated they plan to submit a 505(b)(2) NDA in the eCTD format. In addition, PLx will be requesting a pre-NDA meeting with FDA in early Q1 2012 for guidance. FDA recommended that PLx submit a meeting request as soon as possible with their preferred meeting dates to better coincide with planned NDA submission timelines.

3.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS

1) FDA acknowledged that the proposed combination of literature studies and a 28-day GLP oral toxicity study would be considered sufficient nonclinical safety data in support of (b) (4) for the planned NDA submission, but that the adequacy of the data would be a review issue.

2) PLx plans to repeat the 28-day nonclinical study providing a summary of methodological difficulties and the planned adjustments.

3) PLx will submit analytical data regarding the stability of the test solution before and after (b) (4) to address the concern that (b) (4) of the liquid does or does not significantly alter the composition of (b) (4)

4) PLx plans to submit a formal request asking that DNCE seek input from the Botanical Review Team (BRT) regarding the appropriate level of component characterization. PLx will also submit Type IV DMF standards for (b) (4)

5) (b) (4)

4.0 POST MEETING ADDENDUM

(b) (4)

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts during this meeting

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

/s/

ANDREA LEONARD SEGAL
07/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 74290

MEETING MINUTES

inVentiv Clinical Solutions, LLC
Attention: Jennifer L. Wike
Regulatory Consultant
Authorized Representative for PLx Pharma Inc.
9186 Six Pines Drive, Suite 150
The Woodlands, Texas 77380

Dear Ms. Wike:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PL 2200 (aspirin) capsules, 325 mg.

We also refer to the meeting between representatives of your firm and the FDA on September 23, 2010. The purpose of the meeting was to discuss the regulatory status of (b) (4) as an inactive ingredient and the acceptability of the following chemistry, manufacturing, and control activities for your proposed aspirin drug product:

- The proposed pesticide and aflatoxin testing, characterization, stability, and acceptance criteria for (b) (4)
- The validated PL 2200 drug product dissolution methodology
- The proposed PL 2200 drug product specification and limits for assay and impurities
- The proposed PL 2200 drug product registration stability protocol and amount of stability data needed for the filing of an NDA application

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	Thursday, September 23, 2010 10:00 A.M. to 11:00 A.M., EDT
Meeting Location:	FDA/White Oak 10903 New Hampshire Avenue Building 22, Room 1415 Silver Spring, MD 20993
Application Number:	IND 074290
Product Name:	PL 2200 (325 mg aspirin) capsules
Indication:	Pain Reliever/ Fever Reducer
Sponsor/Applicant Name:	PLx Pharma Inc.
Meeting Chair:	Andrea Leonard-Segal, M.D., M.S. Division Director Division of Nonprescription Clinical Evaluation
Meeting Recorder:	James Lee, PharmD Regulatory Project Manager Division of Nonprescription Clinical Evaluation

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation
Andrea Leonard-Segal, M.D. M.S., Director
Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Medical Team Leader
Priscilla Callahan-Lyon, M.D., Medical Officer
Wafa Harrouk, Ph.D., Pharmacologist/Toxicologist
Melissa Furness, Chief, Project Management Staff
Neel Patel, PharmD., Regulatory Project Manager
James Lee, PharmD., Regulatory Project Manager

Office of New Drug Quality Assessment,
Eric Duffy, Ph.D., Director, Division III
Swapan De, Ph.D., Pharmaceutical Assessment Lead
Olen Stephens, Ph.D., CMC Reviewer
Tien Mien Chen, Ph.D., Biopharmaceutics Reviewer

Office of Compliance, Division of New Drusg and Labeling Compliance
Anuj Shah, J.D., M.A., Regulatory Counsel

SPONSOR ATTENDEES
PLx Pharma Inc.
Gary Mossman, Chief Operating Officer
Upendra Marathi, PhD, MBA, Senior Vice President
Jason Moore, MS, MBA, Vice President
Marie Joy Coraza, MS, Regulatory Affairs Manager
(b) (4)

1. BACKGROUND

PLx Pharma Inc. (PLx) submitted a request for a second End of Phase II (EOP II) meeting on May 07, 2010 to discuss the regulatory status of (b) (4) as an inactive ingredient in the proposed drug product, and the acceptability of several chemistry, manufacturing, and control activities. A prior EOP II meeting was held on November 2, 2009 to discuss the development plan proposed by PLx to support a 505(b)(2) NDA application for PL 2200. A pre-IND meeting was held on September 7, 2007 to discuss PLx's proposal to develop a 325 mg aspirin/ (b) (4) phosphatidylcholine (Aspirin-PC) drug product.

The Agency's preliminary responses to the questions contained in PLx's May 7, 2010 meeting background package were provided to PLx via e-mail on September 21, 2010. These preliminary responses appear in italics below. Following introductions, the meeting agenda consisted of a discussion regarding questions 1, 2, 6, and 7. For questions where no additional discussion is indicated, neither PLx nor FDA raised any additional issues pertaining to these questions.

2. DISCUSSION

QUESTIONS:

1. Soy Lecithin is a component of PL2200 that does not furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals. The sponsor is proposing no claims or implied claims related to the presence of lecithin in the planned 505(b)(2) NDA. Likewise, the sponsor has stipulated the function of lecithin in the drug product (b) (4) and has demonstrated both pharmacokinetic and pharmacodynamic bioequivalence to reference aspirin, as described herein.

   Does the Agency agree, per 21CFR 210.3, 21CFR201.117, 40CFR63.12512, 21CFR310.1(e), that soy lecithin is an inactive ingredient and excipient in the PL2200 drug product?

   FDA Preliminary Response:

   The information provided supports the designation of (b) (4) *as an inactive ingredient. As an inactive ingredient,* (b) (4) *should offer no pharmaceutical activity. Therefore, no claims should be made as to increased safety or efficacy of this drug based on the presence of* (b) (4) *within the drug product. The level of* (b) (4) *to be included in the drug product is* (b) (4) *the approved allowed excipient level. You will need to provide data justifying the planned level of* (b) (4) *including data regarding the safety of* (b) (4) *at this level as an inactive ingredient in a drug product. We also remind you of the previous concerns stated in the November 2, 2009 meeting:*
   "You will also need to show evidence that there is no effect of phosphatidylcholine on the pharmacokinetics or pharmacodynamics of aspirin. Pharmacodynamic endpoints such as COX activity, prostaglandin concentration or platelet activity could be used to show whether aspirin PC is equivalent in its PD profile to aspirin alone. Such data could be obtained from either animal models or incorporated into the clinical protocol."

   Discussion
   PLx asked FDA for further clarification on the specific safety data needed to support approval of their proposed drug product. FDA stated that there is an underlying issue regarding (b) (4) (b) (4) PLx claims that Phosal®35SB is an inactive ingredient in the proposed drug product.

FDA requested PLx to discuss the function of [redacted] in the proposed drug product. PLx responded by stating that [redacted] (phosphatidylcholine) acts as [redacted]

FDA asked PLx to explain the drug product's effects on the human body. PLx responded that PL 2200 does not alter the pharmacokinetic or pharmacodynamic profile of aspirin. [redacted] current PK/PD studies have revealed no changes in the platelet aggregation and thromboxane levels.

FDA expressed a concern regarding the extrapolation of data from PLx's *in vitro* study to *in vivo* settings, and recommended that PLx conduct an *in vivo* study with a control group to properly characterize the effects of [redacted] on the PD and PK profile of aspirin. PLx asked if the suggested *in vivo* study is needed to assess only the anti-platelet effect. FDA responded that in addition to platelet aggregation, COX activity, and prostaglandin concentration, PLx should analyze all routine endpoints that are usually requested in a general toxicology study.

PLx commented that both a 7-day human gastrointestinal toxicity study and a fasting bioequivalence study with PL 2200 revealed no difference in pharmacology profile or adverse events when compared to aspirin. PLx asked FDA if the data provided in these studies would be sufficient to support [redacted] as an inactive ingredient. FDA responded that the concentration of [redacted] is [redacted] than the allowable limits for an inactive ingredient in a drug product, and that it is the responsibility of PLx to provide nonclinical and clinical safety data to demonstrate that this [redacted] concentration of [redacted] is safe. PLx stated that [redacted] has a GRAS status in foods. FDA reiterated that PLx's claim of [redacted] as a GRAS ingredient in foods is not sufficient to prove that th [redacted] s necessarily safe to be used in a drug product. FDA added that all data to support the use of [redacted] as a GRAS ingredient in food products could be submitted for FDA review (including genotoxicity, reproductive/developmental toxicity and carcinogenicity potential). FDA added that exposure in nonclinical studies needs to be sufficient to support the proposed dose and duration of any clinical trial.

FDA reminded PLx that they need to address the safety of chronic use of their aspirin product. Even though the product is labeled for only 10 days of use per dosing course, the product is apt to be used for greater than six months over a lifetime by OTC consumers. PLx asked if the Agency is recommending a 6-month chronic toxicity study. FDA responded that the Agency can not comment on the length of a study at

this time. This decision will be made after a comprehensive review of data on [(b) (4)] has been submitted to and reviewed by the Agency.

2. Extensive characterization has been conducted on the [(b) (4)] excipient to support drug product formulation development. [(b) (4)] is considered GRAS and is compliant with the monograph for Lecithin, NF. In addition to monograph testing, we further characterized the product for phosphatidylcholines content, stability and other quality attributes. Although the lecithin monograph includes determination of the acetone insoluble matter to characterize the phospholipids composition, an HPLC assay has been developed by the sponsor to provide improved specificity for identity, quality, strength and purity of the principal phospholipid in the [(b) (4)] product. Based on the characterization data, the proposed specifications will be used for release. PLx believes that the proposed acceptance criteria are adequate to ensure the quality of [(b) (4)] for use in the commercial PL2200 drug product.

Does the FDA agree?

FDA Preliminary Response:

We do not consider [(b) (4)] to be a GRAS ingredient for drug products (see also responses to question 1).

The batch analyses of three [(b) (4)] lots indicate variability in phospholipid distribution. Also, acceptance criteria for various classes of phospholipids are set as maximum or minimum values, rather than a range. Because you claim that [(b) (4)] is a [(b) (4)], acceptance criteria should be expressed as defined ranges, which assures product quality. Alternatively, you need to provide justification for why certain [(b) (4)] attributes are not critical to the manufacture of your drug product. Manufacturing development studies used to identify critical attributes and acceptance criteria should be described in detail in your NDA application.

Your HPLC method for identifying the identity and composition of the phospholipids in [(b) (4)] appears to be an improvement over compendial identity tests. At thi nnot comment further without more details regarding the method and its validation.

Your stability data indicate variability either in the analytical method or in [(b) (4)] composition. For example, the PC concentrations for Lot #60691 under long-term stability conditions vary from [(b) (4)] for 6 months, 9 months, 12 months, and 18 months respectively. Stability

data will be reviewed in its entirety at the time of NDA submission, but this initial data should encourage further examination of the analytical method.

Finally, we recommend that you provide a proper letter of authorization for any drug master files (DMFs) that you intend to reference as part of your application or provide complete CMC information for (b) (4) *to support the application, at the time of NDA submission.*

Discussion

PLx sought clarification regarding the Agency's preliminary comments asking for complete CMC information fo (b) (4) to support an NDA. FDA responded by stating that PLx needs to establish acceptance criteria for (b) (4) components with upper and lower acceptance criteria, and identify the origins of raw materials.

3. The FDA has previously requested documentation that the (b) (4) soy lecithin is pesticide free. The current lecithin excipient source is (b) (4) (b) (4) The manufacturer of (b) (4) provides testing on a per-lot basis using the General Method for Pesticide Residues Analysis described in USP <561> Articles of Botanical Origin demonstrating that this material is free from pesticides. In addition, to ensure absence of aflatoxins, each lot could be tested using the Test for Aflatoxins described in USP <561>.

Does the FDA agree that the information presented in the briefing package is adequate to provide assurance that this excipient is free of pesticides?

Does the FDA agree with the sponsor that routine testing (either on a periodic or batch-to-batch basis) for absence of aflatoxins is not required?

FDA Preliminary Response:

Insufficient information is available at this time to address your question. However, if Pesticide Residues Analysis as per USP <561> is included in the vendor's certificate of Analysis (CoA) and your acceptance criteria are based on the vendor's CoA, pesticide testing may not be required for the finished drug product.

The wording of your question is ambiguous regarding Aflatoxin testing. From your proposed specifications for the PL 2200 drug product, Aflatoxin testing will not be part of your release specifications. Therefore, please clarify whether the (b) (4) *vendor includes a Test of Aflatoxin as per USP <561> on each batch. As with the Pesticide Residues Analysis, if Aflatoxin testing is part of your acceptance criteria and the testing is included on the CoA, additional testing of the drug product would not be necessary.*

4. Proposed specifications for release and registration stability testing of the PL2200 drug product are presented in the briefing document.

   Does the FDA agree that the proposed tests are adequate to ensure the quality of the drug for registration?

   FDA Preliminary Response:

   Your stability data for (b) (4) *indicates this component of the drug product* (b) (4) *Since* (b) (4) *constitutes* (b) (4) *of the drug product, release and stability specifications should be set (not just reported for information purposes) regarding the* (b) (4) *composition and any related impurities that result from* (b) (4) *degradation.*

5. **Is the product-specific dissolution method and proposed acceptance criterion developed for the PL2200 drug product suitable for use during release and registration stability testing?**

   FDA Preliminary Response:

   Based on the provided information, your proposed dissolution method is not adequate. (b) (4) *You did not provide dissolution data/profiles to demonstrate the discriminating power of the proposed methodology and justification to support your claim.*

   You need to provide the dissolution development report and dissolution data/profiles (i.e., selection of the equipment/apparatus, agitation/rotation speed, in vitro dissolution media of different pHs, assay, sink conditions, surfactants added, etc.). To obtain feedback from the Agency, please submit: 1) the dissolution development report, 2) the needed dissolution data/profiles, and 3) your justification and conclusion for the selection of the proposed dissolution methodology and specifications.

6. Per the USP Monographs for Aspirin Tablets, Capsules, Delayed Release Capsules, and Effervescent Tablets for Oral Solution, the free salicylic acid limits for these aspirin dose forms are 0.3%, 0.75%, 3.0% and 8.0%, respectively. Stability data for the PL2200 drug product provided in the briefing package demonstrates that the free salicylic acid content is comparable with these commercial products. PLx is considering an (b) (4) free salicylic acid limit for the commercial PL2200 drug product.

Does the FDA agree that an (b) (4) free salicylic acid limit at expiry is appropriate?

FDA Preliminary Response:

Refer to the Meeting Minutes for the September 7, 2007 type B meeting. The appropriate limit for salicylic acid would be a review issue. We would consider salicylic acid levels found in the stability studies, in addition to the allowed limit in the USP. At the time of NDA submission, you should propose an appropriate limit for salicylic acid along with a justification for this specification in 3.2.P.4.4 based on clinical safety issues and stability data.

Discussion

PLx asked for clarification regarding the types of variables that would be reviewed to determine the appropriate limit of free salicylic acid in their drug product. FDA responded by asking why PLx has chosen the (b) (4) limit versus the (b) (4) limit for capsule dosage forms. PLx responded (b) (4) The Agency responded that a full and complete justification for the (b) (4) limit should be included in the NDA. Because PLx had not provided a full justification in advance of the meeting, the Agency was not prepared to comment further.

7. A registration drug product stability protocol is presented in the briefing document. PLx will provide at least 24 months of long-term data for one batch and 6 months of long-term and accelerated data for two additional batches of drug product in the NDA. The remaining registration stability data will be submitted on a rolling basis during review period.

Is the proposed stability protocol adequate to support a 505(b)(2) NDA submission? Is the proposed amount of stability data in the NDA submission acceptable to the FDA for anticipated expiry dating of (b) (4)

FDA Preliminary Response:

Stability data is reviewed upon submission of the NDA. Expiry will be established at that time in light of the stability data and other components of the application (refer to response to question 4 regarding (b) (4) degradation products). At the time of filing of the NDA, we require 12-months of real-time and 6-months of accelerated stability data for three stability batches.

Discussion

PLx sought clarification regarding the Agency's preliminary comments specifying the required stability data for the NDA submission. FDA reiterated that PLx is required

to provide 12 months of real-time stability data and 6-months of accelerated stability data for 3 batches as part of their NDA. PLx asked if it would be acceptable to provide 24 months of long term and 6 months of accelerated stability data for one batch manufactured at pilot scale using the to-be-marketed container closure system, while stability data for two additional batches will be provided in commercial scale. FDA responded that the proposal is acceptable. FDA recommended that PLx submit details of the stability protocol for FDA review and comments prior to the NDA filing.

Additional CMC Comments:

Table 10 contains a proposed testing schedule for the PL 2200 Drug product. The 6-month time point under accelerated conditions should fall under testing regimen "A", which includes testing for Microbial Limits.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

4.0 SUMMARY OF KEY DISCUSSION POINTS:

1. PLx will provide a comprehensive toxicity profile (including animal and human data) for (b) (4)

2. FDA agreed that information contained within the (b) (4) DMF or equivalent information within the NDA would be sufficient regarding the control information, and origins of the raw materials used to manufacture the (b) (4)

3. PLx will provide a justification for choosing (b) (4) versus (b) (4) as the limit for the free salicylic acid capsule dosage form and a discussion of any safety related issues.

4. PLx will submit 12 months of real-time data in addition to 6-months accelerated stability data for 3 batches as part of the NDA.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for this meeting

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

/s/

ANDREA LEONARD SEGAL
10/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 74,290

inVentiv Clinical Solutions, LLC
Attention: Jaye Thompson, Ph.D.
Senior Vice President, Clinical Operations
Authorized Representative for PLx Pharma Inc.
2202 Timberloch Place, Suite 230
The Woodlands, Texas 77380

Dear Dr. Thompson:

Please refer to your Investigational New Drug Application (IND) file for PL 2200 (325 mg aspirin) capsule.

We also refer to the meeting between representatives of your firm and the FDA on November 2, 2009. The purpose of the meeting was to discuss your clinical development plan to support a 505(b)(2) NDA submission for your proposed aspirin formulation.

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

If you have any questions, call Neel Patel, Regulatory Project Manager at (301) 796-0970.

Sincerely,

{See appended electronic signature page}

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

Enclosure- Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	November 2, 2009 10:00 a.m. – 11:00 a.m. EST
Meeting Location:	FDA/White Oak 10903 New Hampshire Avenue Room 1419 Silver Spring, MD 20993
Application Number:	IND 74290
Product Name:	PL 2200 (325 mg aspirin)
Indication:	OTC pain reliever/fever reducer indications
Sponsor/Applicant Name:	PLx Pharma, authorized representative for inVentiv Clinical Solutions
Meeting Chair:	Andrea Leonard-Segal, M.D. Director Division of Nonprescription Clinical Evaluation
Meeting Recorder:	Neel Patel, PharmD. Regulatory Project Manager Division of Nonprescription Clinical Evaluation

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation:
Andrea Leonard-Segal, M.D., Director
Joel Schiffenbauer, M.D., Deputy Director
Priscilla Callahan-Lyon, M.D., Medical Officer
Melissa Furness, Chief, Project Management Staff
Cindy Li, Ph.D., Pharmacologist/Toxicologist
Neel Patel, PharmD., Regulatory Project Manager
James Lee, PharmD., Regulatory Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assessment
Shulin Ding, Ph.D, Chemist, Pharmaceutical Assessment Lead

Division of Clinical Pharmacology II, Office of Clinical Pharmacology:
Suresh Doddapaneni, Ph.D., Deputy Director
Sayed (Sam) Al Habet, Ph.D., Clinical Pharmacology Reviewer

SPONSOR ATTENDEES
inVentiv Clinical Solutions, LLC
LeAnn Latham, Manager, Regulatory Affairs

PLx Pharma Inc.
Ron Zimmerman, President & CEO
Upendra Marathi, Ph.D., Senior Vice President
Jason Moore, MS, MBA, Vice President
(b) (4)

1.0 BACKGROUND

PLx Pharma Inc. (PLx) submitted a request to the FDA for an End of Phase II (EOP II) meeting on July 08, 2009 to discuss the development plan to support a 505(b)(2) NDA for PL 2200, a new (b) (4) oil-based aspirin capsule. A pre-IND meeting was held on September 7, 2007 to discuss the PLx proposal to develop a 325 mg aspirin/(b) (4) phosphatidylcholine (Aspirin-PC) combination drug product. PLx believes the phosphatidylcholine (PC) component in the product (b) (4) The discussion at this meeting focused on the quantity and purpose of phosphatidylcholine in the product.

Subsequently, PLx conducted a bioequivalence study comparing PL 2200 to Bayer aspirin. The October 2, 2009 package for this EOP II meeting states that PLx is (b) (4) PL 2200 would be marketed with the standard OTC pain reliever and fever reducer indications as outlined in the tentative final monograph and PLx considers the role of PC in this product to be as an excipient.

2.0 MEETING OBJECTIVES:

The objectives of this meeting were to discuss and obtain agreement from the FDA on the following:

- PL 2200 consists of one active pharmaceutical ingredient
- The proposed clinical development program for the analgesic/antipyretic labeling for over-the-counter (OTC) aspirin
- The proposed plan for progression to a 505(b)(2) NDA filing

3.0 DISCUSSION:

Preliminary responses to the questions enclosed in the October 2, 2009 Meeting Package were sent to PLx via mail on October 30, 2009. These questions and preliminary FDA responses are listed below in italics.

Following introductions, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA. For questions where no additional discussion is indicated, neither PLx nor FDA raised any additional issues pertaining to these questions at the meeting.

Questions:

1. ***Does FDA agree that the PC-containing oil serves as an excipient in the PL 2200 formulation for the proposed OTC labeled analgesic and anti-pyretic indications of aspirin?***

   FDA Preliminary Response:
   You will need to provide an acceptable justification for the function of phosphatidylcholine as an excipient in this product. You will also need to show evidence that there is no effect of

phosphatidylcholine on the pharmacokinetics or pharmacodynamics of aspirin. The adequacy of the data will be a review issue.

Addition Discussion on Question 1

PLx asked FDA if the justification provided on page 8 of the briefing package for the use of PC as an excipient is acceptable. It is stated on page 8 that PC-containing oil (b) (4) in PL2200. PLx thought that the only requirement for an inactive ingredient was that it did not exhibit any activity or interfere with the activity of the active ingredient.

FDA responded that each inactive ingredient included in the formulation of a drug product should have a function. A scientifically justifiable function for PC as an excipient in PL2200 is expected in the NDA submission. FDA explained that the function of an excipient is usually based on its physical and/or chemical properties. PLx should further elaborate on the proposed function of PC using the physical and chemical properties of PC.

PLx asked FDA's suggestion on additional pharmacodynamic endpoints besides the effects on platelet function. FDA responded that a response will be provided in the post-meeting addendum.

2. ***Will a fasted bioequivalence pharmacokinetic study and the proposed food-effect pharmacokinetic study (PL-ASA-003), in addition to cross-references to the Agency's previous finding of safety and effectiveness of immediate-release aspirin, serve as sufficient clinical basis for a 505(b)(2) NDA for the intended analgesic/antipyretic labeling (same as for OTC aspirin products)?***

FDA Preliminary Response:

The proposed food effect study appears adequate. The pharmacokinetic study (PL-ASA-001) demonstrated bioequivalence at the 650 mg dose but not the 325 mg dose. You will need to provide a rationale for why this difference is not of clinical concern.

Addition Discussion on Question 2

PLx asked FDA if they had a clinical safety concern for the lower dose since it did not show bioequivalence with respect to Cmax. PLx also asked if additional pharmacokinetic data would be needed since bioequivalence was shown at the higher 650 mg dose.

FDA responded that PLx should provide a rationale for the increased exposure at the 325 mg dose in the study and why the difference is not of clinical concern. FDA added that if PLx believes there is no safety or efficacy issue, then the NDA submission should provide support for this in detail.

FDA advised PLx to provide a rationale for the lack of bioequivalence at the 325 mg dose when the same product showed bioequivalence at the 650 mg dose. It was pointed out that Subject 106 appears to be an outlier and may have contributed to observed lack of bioequivalence. FDA asked PLx to further investigate data for this subject to see if there is an explanation for the relatively high exposure seen with this subject for the Aspirin-PC treatment.

3. Is the bioequivalence of PL 2200 demonstrated at the highest dose (650 mg) in study PL-ASA-001, and supported by the pharmacokinetic data at the lower 325 mg dose, sufficient to demonstrate comparability to immediate-release aspirin under fasting conditions?

FDA Preliminary Response:

The 325 mg dose of PL 2200 did not meet the established criteria for bioequivalence. Whether the pharmacokinetic data provided will be sufficient for approval of the product will be a review issue.

4. Does FDA agree that a cross-over food-effect pharmacokinetic study using a dose of 650 mg (as aspirin in PL 2200), as outlined in the proposed protocol PL-ASA-003, is the appropriate study design to complement the fasting pharmacokinetic bioequivalence study (PL-ASA-001) and if successful will complete the clinical program for PL 2200 to obtain marketing approval for the analgesic/anti-pyretic indications as part of a 505(b)(2) NDA?

FDA Preliminary Response:

The cross-over food-effect PK study using the 650 mg dose as outlined in the proposed protocol PL-ASA-003 will complement the fasting bioequivalence study PL-ASA-001 and, if successful, will complete the clinical pharmacology program. Please also refer to our response to Question 2 and the Additional Comments below.

Additional Comments:

We suggest the following changes to the proposed protocol PL-ASA-003 (the food-effect study:

- *Consider a one week washout period instead of three days.*
- *Establish and state the maximum age of subjects to be enrolled in the study.*
- *Specify how many subjects are expected to complete the study. You provide the enrolled number as 20 subjects.*
- *Exclude subjects that have taken any prescription medications within the last 14 days (not the three days as currently proposed).*

We also remind you that you can not rely on the Internal Analgesic, Antipyretic, and Antirheumatic Drug Products Tentative Final Monograph (IAAA TFM) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm070484.htm) to support the safety and efficacy of your proposed aspirin product. We refer you to 21 CFR 330.11. However, you may rely on pertinent, publicly available information such as literature, postmarketing safety databases, or data contained in the finalized Monograph documents such as Aspirin Professional Labeling (see 21 CFR part 343) for preclinical and relevant safety information. You will need to provide data which may be from published literature, among other sources, that supports the safety and efficacy of your product or of the reference product to which your product is bioequivalent.

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

We also refer you to the following Guidances for Industry: How to Comply with the Pediatric Research Equity Act
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf

Additional Discussion on Question 4

PLx asked FDA for further clarification on the appropriate resources to reference the safety and efficacy of their proposed product. PLx stated that they are having difficulty locating references that provide aspirin analgesic data.

FDA responded that PLx could refer to publicly available information such as medical and scientific literature and data contained in the finalized monograph documents such as the professional labeling for aspirin. FDA explained that the Advanced Notice of Proposed Rulemaking for internal analgesics may include appropriate references that PLx can use to support the conclusion that aspirin is safe and effective as an OTC analgesic at the recommended doses.

FDA added that efficacy and safety data for each separate pain indication would not be required. Data for two different pain indications from well-conducted studies would be sufficient to receive all of the OTC pain indications with the exception of the menstrual pain indication. FDA further commented that data to support the fever indication should also be provided. FDA stressed that PLx should provide, in total, a reasonable body of evidence to support the safety and efficacy of aspirin as an OTC pain reliever/fever reducer.

PLx confirmed their understanding by adding that, cardiovascular studies may be used to support safety data, but can not be utilized for pain efficacy.

Future Development Questions

FDA Response:
Since questions 5 and 6 are outside the scope of your meeting request, we are not providing comments to these questions at this meeting.

5. (b) (4)

(b) (4)

6. (b) (4)

Additional Discussion on Future Development Questions

(b) (4)

4.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS:

1. PLx will provide a scientifically justifiable function for phosphatidylcholine as an excipient based on physical/chemical properties.

2. PLx will provide a rationale as to why the 325 mg dose of PL 2200 does not meet the bioequivalence standards in their study and why this difference is not of clinical concern.

3. FDA will provide further clarification on additional pharmacodynamic endpoints in a post-meeting addendum.

4. PLx may utilize well-conducted studies in the published literature to support the safety and efficacy of aspirin for the pain and fever indications. FDA agreed that safety and efficacy demonstrated on two different OTC pain models would be needed to receive all the of the aspirin indications in the TFM except the menstrual pain indication. Data from well-conducted studies targeting menstrual pain are needed to support that indication; these could be from the published literature.

5.0 POST-MEETING ADDENDUM:

Pharmacodynamic endpoints such as COX activity, prostaglandin concentration or platelet activity could be used to show whether aspirin PC is equivalent in its PD profile to aspirin alone. Such data could be obtained from either animal models or incorporated into the clinical protocol.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-74290	GI-1	PLX PHARMA INC	ASPIRIN PC

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/s/

ANDREA LEONARD SEGAL
11/30/2009

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PIND 74,290

SYNERGOS, Inc.

Attention: Jaye Thompson, Ph.D.
President
Agent for PLx Pharma Inc.
2202 Timberloch Place, Suite 230
The Woodlands, Texas 77380-1109

Dear Dr. Thompson:

Please refer to your Pre-Investigational New Drug Application (PIND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aspirin-PC.

We also refer to the meeting between representatives of your firm and the FDA on September 7, 2007. The purpose of the meeting was to discuss your proposal to develop an oil-based aspirin formulation (b) (4)

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Neel Patel, Regulatory Project Manager, at (301) 796-0970.

Sincerely,
{See appended electronic signature page}

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

Enclosure

Meeting Type:	Type B
Meeting Category:	Pre-IND
Meeting Date and Time:	September 7, 2007 9:00 a.m. – 10:00 a.m. EST
Location:	FDA/White Oak 10903 New Hampshire Avenue Room 1421 Silver Spring, MD 20993
Application:	PIND 74,290
Product Name:	Aspirin-PC
Received Briefing Package:	August 6, 2007
Sponsor Name:	PLx Pharma Inc.
Meeting Requestor:	Jaye Thompson, Ph.D. President, SYNERGOS, Inc. Agent for PLx Pharma Inc.
Meeting Chair:	Andrea Leonard-Segal, M.D. Director Division of Nonprescription Clinical Evaluation
Meeting Recorder:	Robin Anderson, R.N., M.B.A. Regulatory Project Manager Division of Nonprescription Clinical Evaluation

Meeting Attendees:

FDA Attendees:

Division of Nonprescription Clinical Evaluation*:*
Andrea Leonard-Segal, M.D., Director
Joel Schiffenbauer, M.D., Deputy Director
Bindi Nikhar, M.D., Medical Team Leader
Steve Osborne, M.D., Medical Reviewer
Christina Chang, M.D., Medical Reviewer
Wafa Harrouk, Ph.D., Pharmacologist/Toxicologist
Leah Christl, Ph.D., Chief, Project Management Staff
Neel Patel, PharmD., Regulatory Project Manager
Robin Anderson, R.N., M.B.A., Regulatory Project Manager

Division of Nonprescription Regulation Development:
Michael Koenig, Ph.D., Interdisciplinary Scientist

Office of Clinical Pharmacology:
Srikanth Nallani, Ph.D., Clinical Pharmacology Reviewer

Division of Pharmaceutical Science, Office of New Drug Quality Assessment:
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead

Division of Cardiovascular and Renal Products:
Thomas Marciniak, M.D., Acting Deputy Director

Division of Gastroenterology Products:
Ruyi He, M.D., Medical Team Leader

External Constituent Attendees:

SYNERGOS, Inc.:
Lawrence Goldkind, M.D., Consultant
Sharon Heddish, Consultant
Jaye Thompson, Consultant
Jennifer L. Wike, Consultant

PLx Pharma Inc.:
Ron Zimmerman, President
Lenard Lichtenberger, Ph.D., CSO
Upendra Marathi, Ph.D., Supervisor

1.0 BACKGROUND:

PLx Pharma Inc. submitted a meeting request to the FDA for a Pre-IND meeting on June 19, 2007 to discuss their proposal to develop an oil-based aspirin formulation (b) (4)

According to Plx Pharma's August 3, 2007 meeting package, Aspirin-PC (ASA-PC) is an oil-based aspirin formulation containing 325 mg of aspirin with (b) (4) of (b) (4) (b) (4) soy phosphatidylcholine (PC) (b) (4) excipient]. PC is also known as lecithin. Lecithin is GRAS as a food ingredient and is a National Formulary recognized pharmaceutical excipient.

PLx Pharma is seeking the pain reliever/fever reducer indication for aspirin outlined in the tentative final monograph for OTC internal analgesic products (b) (4) PLx Pharma stated in their meeting package that lecithin in the proposed product (b) (4)

1.1 MEETING OBJECTIVES:

The objective of this meeting was for PLx Pharma to obtain guidance from the Agency for the proposed regulatory path for Aspirin-PC, including discussion of the:

- clinical development program
- proposed study design
- feasibility of a 505(b)(2) application

2.0 DISCUSSION:

Preliminary responses to the questions enclosed in the August 3, 2007 meeting package were sent to Synergos, the agent for PLx Pharma Inc., via e-mail on September 6, 2007. These questions and preliminary FDA responses are listed below in italics.

Following introductions, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA. For questions where no additional discussion is indicated, neither PLx Pharma nor FDA raised any additional issues pertaining to these questions at the meeting.

2.1 General Comments by FDA:

In your meeting package, you note that you are seeking OTC consumer labeling similar to other OTC aspirin products as outlined in the tentative final monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human

Use to include the pain reliever and fever reducer uses. (b) (4) [redacted]

(b) (4) [redacted]

2.2 Regulatory Path for Approval of Aspirin-PC:

Question 1:

The Sponsor proposes a bioequivalence study to compare the single dose pharmacokinetics of the test compound Aspirin-PC to aspirin and that study will be the basis of a 505(b)(2) NDA. This NDA will rely substantially upon the Agency's previous determination of the safety and effectiveness of aspirin. The only single agent Rx or OTC aspirin product on the market in the Orange Book is a 500 mg tablet of Bayer Extra Strength Aspirin for Migraine Pain. Is it appropriate to use a 325 mg Genuine Bayer® Aspirin tablet as a comparator for this study? If not, what is the appropriate reference drug?

FDA Preliminary Response:

Any marketed 325 mg aspirin product that meets the requirements outlined in the tentative final monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use is an appropriate reference drug product. We also refer you to our response to Question 2 below.

Question 2:

If the pharmacokinetic study with the Aspirin-PC formulation shows bioequivalence to Genuine Bayer® Aspirin, would the proposed bioequivalence study (see Appendix B) be sufficient to support a 505(b)(2) application for over-the-counter (OTC) dosing of Aspirin-PC for the OTC monograph indications (21CFR 343.80, see Section 1.2)? If not, what additional studies would be required to support approval for Aspirin PC with the current indications (b) (4) [redacted] ***for aspirin products?***

FDA Preliminary Response:

(b) (4) *The indications being sought for the proposed new product would determine to which division your NDA should be submitted.*

- *To obtain the over-the-counter (OTC) pain reliever/fever reducer indications* (b) (4) *you would need to submit an application to the Division of Nonprescription Clinical Evaluation..* (b) (4)

  You would need to demonstrate that PC does not interfere with the action of aspirin as a pain reliever/fever reducer. We also remind you that you cannot rely on the tentative final monograph for aspirin to support the safety and efficacy of your product. We refer you to 21 CFR 330.11.

- (b) (4)

  As explained above in the General Comments, (b) (4)

In addition to testing for bioequivalence under fasting conditions, effect of food on the formulation should also be tested.

Additional Discussion on Question 2

PLx Pharma asked FDA to explain the rationale for considering (b) (4) PLx Pharma mentioned that (b) (4) (b) (4)

FDA responded that one reason PC is considered (b) (4) FDA stated that, as proposed in PLx Pharma's briefing document, the PC component (b) (4) aspirin, (b) (4) (b) (4) FDA explained that as proposed by PLx Pharma, the product (b) (4) FDA also noted that PC is not a known excipient recognized in combination with ASA, which makes it a novel product. (See the post-meeting addendum, below.)

PLx Pharma asked FDA if an NDA would be required (b) (4) the indications were limited to those specified in the tentative final monograph for aspirin.

FDA noted that since this proposal was not mentioned in the briefing package, further details regarding the requirements to support this proposal would need internal discussion and would be provided in a post-meeting addendum. FDA did state that if Plx Pharma chose to market their product as 'Aspirin-PC', (b) (4) They would need to address the safety question of the possible antiplatelet activity for the PC.

PLx Pharma asked FDA how they could demonstrate that PC is (b) (4)

FDA responded that they were not prepared to provide a response and would address that question in a post meeting addendum.

(b) (4)

FDA responded that a pharmacokinetic (PK) approach to demonstrate that PC does not interfere with the bioavailability of aspirin would be acceptable for the OTC pain reliever/fever reducer indications. FDA added that clinical safety and efficacy studies would be required if bioequivalence is not demonstrated. (b) (4)

(b) (4)

FDA responded that separate NDA's should be submitted for the OTC (pain reliever/fever reducer (b) (4) (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

FDA responded that PLx Pharma should request a Pre-IND meeting with [redacted] (b) (4)

PLx Pharma asked FDA if the Office of Compliance would allow another GRAS product on the market. FDA responded that PC is GRAS only as a food ingredient, not as a drug.

2.3 Bioequivalence Clinical Trial Protocol:

Question 3:

The Sponsor is proposing a 28 healthy human subject study that will test the bioequivalence of Aspirin-PC (ASA-PC) containing 325 mg of aspirin (ASA) at two dose levels (325 mg and 650 mg) with 14 patients at each dose level in a crossover design. See draft protocol in Appendix B. Is this sample size acceptable to demonstrate bioequivalence? If not, what is the appropriate sample size?

FDA Preliminary Response:

Sample sizes should be based on statistical power calculations taking into account known aspirin pharmacokinetics. (See Guidance for Industry: Statistical Approaches to Establishing Bioequivalence)

Question 4:

The Sponsor plans to analyze pharmacokinetic samples in order to assess bioequivalence of Aspirin-PC to aspirin. As acetylsalicylic acid (ASA) is rapidly hydrolyzed to the primary metabolite salicylic acid within 10-15 min of oral administration (see Appendix C) rendering the analysis of ASA impractical, the Sponsor plans to assess the bioequivalence based on aspirin's primary metabolite, salicylic acid. Is salicylic acid the appropriate analyte to assess bioequivalence?

FDA Preliminary Response:

It is acceptable to assay salicylic acid as the analyte for bioequivalence.

Question 5:

The Sponsor proposes to compare the ex vivo arachidonic acid and collagen induced platelet aggregation between Aspirin-PC and aspirin to confirm the anti-platelet

activity of Aspirin-PC. The Sponsor does not plan to measure Thromboxane B2 as a surrogate marker of anti-platelet activity. Is the measurement of Thromboxane B2 necessar (b) (4)

FDA Preliminary Response:

You should discuss your development plan (b) (4) *We also refer you to our response to Question 2 above.*

2.4 Chemistry, Manufacturing and Controls:

Question 6:

The Sponsor proposes a specification of not more tha (b) (4) ***salicylic acid present in an ASA-PC hard shelled capsule over the shelf-life of the product*** (b) (4) ***The salicylate limit for Aspirin Effervescent Tablets for Oral Solution is "not more than 8%" (USP 30, 2007). A*** (b) (4) ***level of salicylic acid over time will not affect the safety of the product because salicylic acid is the primary in vivo metabolite of aspirin. Does the Agency agree thi*** (b) (4) ***limit is an appropriate benchmark to determine the shelf-life of Aspirin-PC? If not, what is the appropriate limit of the presence of salicylic acid for an oil-based aspirin formulation?***

FDA Preliminary Response:

No, we do not agree. The shelf-life of a product is determined by drug product specification which consists of a list of test parameters. The product must conform to the acceptance criteria of all test parameters during the shelf-life. Therefore, we cannot agree with your proposal that the shelf-life of the proposed product is determined by (b) (4) *of salicylic acid.*

The appropriate limit for salicylic acid would be a review issue. We would consider salicylic acid levels found in the stability studies, in addition to the allowed limit in the USP.

Additional Comments:

A full CMC information package is expected to be available in the IND for phosphatidylcholine. Alternatively, you can reference a DMF in the IND with a letter of authorization.

Additional Discussion on Questions 6:

PLx Pharma asked FDA how to define what PC is and how to characterize it. PLx Pharma stressed that PC (b) (4) and that it is difficult to get a dissolution profile for it.

FDA responded that full CMC information including the complete composition for PC should be provided. FDA noted that NDAs of approved liposomal drugs require quantitation of each phopholipid involved. Therefore, technologies for characterization and quantitation of PC exists. FDA added that dissolution could be discussed once the composition and analytical information is submitted.

2.5 (b) (4)

Question 7:

(b) (4)

FDA Preliminary Response:

Since you have not submitted a protocol for our consideration, we cannot make any commitments based on your submission. However, please see our responses below.

(b) (4)

FDA Preliminary Response:

Your proposal appears acceptable.

b. Can such data form the basis fo (b) (4) ***If not, what type of clinical endpoint is required to obtain*** (b) (4) (b) (4)

FDA Preliminary Response:

Such a claim is data dependent. It should be noted that a (b) (4)

Additional Discussion on Question 7:

(b) (4)

2.6 Special Populations:

Question 8:

Due to the potential risk of aspirin inducing Reye's syndrome in children, the Sponsor proposes requesting a waiver to exclude children from the bioequivalence study. Does the Agency agree?

FDA Preliminary Response:

Children may be excluded from the proposed bioequivalence study. However, per the tentative final monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use, aspirin is labeled down to the age of two years. (b) (4)

3.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS:

1. (b) (4)

2. PLx Pharma will discuss their development plan to [redacted] (b) (4)

3. For the aspirin pain reliever/fever reducer claims [redacted] (b) (4) (See post-meeting addendum.)

4. PLx Pharma agreed to provide protocols for FDA review and comment for the over-the-counter claims.

5. FDA agreed to provide advice on an Aspirin-PC product t[redacted] (b) (4) as a post-meeting addendum.

6. FDA agreed to provide advice on how to demonstrate that PC is not an active ingredient as a post-meeting addendum.

4.0 POST-MEETING ADDENDUM:

[redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

(b) (4)

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/s/

Andrea Segal

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