

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203697Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	1/14/13
<b>From</b>	Joel Schiffenbauer, MD
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA/BLA #</b>	NDA 203697
<b>Supplement #</b>	
<b>Applicant Name</b>	PLx Pharma
<b>Date of Submission</b>	3/12/12
<b>PDUFA Goal Date</b>	1/14/13
<b>Proprietary Name / Established (USAN) Name</b>	To be determined aspirin
<b>Dosage Forms / Strength</b>	capsule
<b>Proposed Indication(s)</b>	1. Temporary relief of minor aches and pains 2. fever
<b>Action/Recommended Action</b>	<i>approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review DNCE	L. Hu
DAAP	C. Fang/S. Hertz
DCRP	T. Marciniak
Statistical Review	
Pharmacology Toxicology Review	C. Li/P. Brown
CMC Review/OBP Review	M. Ramaswamy/ S. De
Biopharm	A. Chen/A. Dorantes
Microbiology Review	
Clinical Pharmacology Review	S. Naraharisetti/ Y. Xu; D. Menon-Andersen
DNRD labeling	E. Abraham/S. Adah
DSI	
CDTL Review	D. Shetty
OSE/DMEPA	A. Tu/T. Bridges
OSE/DDRE	
OSE/DSRCS	
Other Botanicals	J. Dou/S.T. Chen

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

# Signatory Authority Review Template

## 1. Introduction

Aspirin (acetylsalicylic acid) is a non-narcotic analgesic with anti-inflammatory and anti-pyretic activity. Aspirin products have been marketed worldwide for medicinal use since the 1800s. Inhibition of prostaglandin biosynthesis appears to account for most of its clinical effect. Following absorption, aspirin is hydrolyzed to salicylic acid which is considered the active metabolite for its major clinical effects. Aspirin also inhibits platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase.

Aspirin is considered a pain reliever and fever reducer in the OTC Tentative Final Monograph (hereafter "TFM") for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (53 Federal Register, 46204, Nov. 16, 1988). The proposed labeled indications for Aspirin-PC (this product) are identical to the indications outlined in the TFM for OTC internal analgesic products as follows: for temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, premenstrual and menstrual cramps; for temporarily reducing fever. In addition, aspirin is included in a FM under 21 CFR 343 for the prevention of cardiovascular events and the treatment of rheumatologic disorders.

## 2. Background

PLx Pharma Inc. submitted NDA 203697 as a 505(b) (2) application for Aspirin-PC capsules (325-mg) for Over-The-Counter (OTC) use. 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. Lecithin is chiefly composed of a lipid component phosphotidylcholine (PC). (b) (4)

(b) (4). For this submission, the applicant seeks (b) (4) the claims found in the TFM as described above.

The applicant pursued the b2 route rather than the monograph route for aspirin, due to the fact that the Aspirin-PC formulation contains (b) (4) lecithin (b) (4) not present in any approved product at that level and not present in any product in any monograph). For an appropriate reference drug for this 505(b) (2) application, the applicant chose to compare themselves to a marketed 325-mg aspirin product that meets the requirements outlined in the TFM, in accordance with discussions with the Agency. Therefore, the applicant used Bayer Aspirin tablets, 325-mg as a reference drug in their pivotal bioequivalence studies.

No specific clinical safety and efficacy studies have been submitted for this product and the applicant is relying on the safety and efficacy of aspirin based on literature references (and the final monograph for aspirin).

This review will summarize the findings from chemistry, pharm/tox, and clin pharm reviewers, as well as safety and pediatric related issues.

### 3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections are pending at this time. Stability testing supports an expiry of 18 months. There are no other outstanding issues.

The following is extracted from the CMC review:

*From CMC perspective, this NDA is recommended for approval. The CMC recommendation does not incorporate any potential facility inspection issues. As of 12/10/12, an overall recommendation from the Office of Compliance is pending. A shelf-life of 18 months is recommended for product packaged in HDPE bottles with desiccant or in blisters, when stored at 25± 2°C/60% RH.*

*The NDA describes adequately the composition of the drug product, lists all components used in the manufacture of the drug product, the specifications for each component, and provides adequate reference to DMF for all excipients and packaging components used in the manufacture of drug product.*

*The NDA also provides reference to the current edition of the U.S. Pharmacopeia, and the National Formulary for components (lecithin, MCT oil, anhydrous citric acid, colloidal silicon dioxide) associated with this NDA. The proposed specification for accepting soy lecithin (b) (4) the expectation of USP monograph specification provided for soy lecithin.*

*The levels of all components used in the PL2200 drug product do not exceed the found in inactive ingredients database for oral products. Soy lecithin is considered GRAS and is permitted as a food additive and therefore is acceptable.*

*The Applicant has proposed adequate in-process tests for the proposed process, which includes (b) (4)*

*The NDA contains specifications necessary to ensure the identity, strength, quality, purity, and potency, of the drug product . The proposed specification for Aspirin capsules includes appearance, identity by UV and HPLC, assay, impurities, (b) (4) dissolution, content uniformity per USP<905>, and microbial enumeration test (USP<61> and <62>. In addition , the Applicant has included a test for monitoring the levels of*

(b) (4)

(b) (4)

*The NDA contains 18 months of real-time stability data , 12 months of intermediate stability data and 6 months of accelerated stability data for three primary batches packaged in HDPE bottles and 1 batch of product packaged in blister containing (b) (4). Based on available stability data for primary batches, a shelf-life of 18 months is recommended for PL2200 Aspirin capsules packaged in 75cc and 250 cc bottles with desiccant and in blisters with (b) (4) film when stored under a controlled temperature  $25 \pm 2^{\circ}\text{C}/60\%RH$ .*

The Botanical reviewer supports the chemistry evaluation and writes:

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

## 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

The following is extracted from the pharmacology/toxicology review:

*No pivotal toxicology studies were conducted or submitted with PL2200 for the present NDA. The nonclinical safety of aspirin refers to the data and information supporting the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use. The applicant, PLx Pharma Inc., has provided a review of the more recent published scientific literature on the nonclinical safety of aspirin. Overall there are no novel findings or unexplained toxicity observed.*

*There are two issues noticed during the current nonclinical review with regards to the excipients and impurities/degradants of the drug product:*

*(1) The proposed drug product contains (b) (4) in the formulation. The applicant claims (b) (4) is lecithin and functions as an inactive ingredient. The evaluation by ONDQA review team and Botanical Review Team (BRT) confirmed that (b) (4) is consistent with the lecithin USP monograph (Refer to the NDA review and memorandum by*

ONDQA and BRT reviewers for the present NDA). Based on this information, the evaluation of (b) (4) (lecithin) in PL2200 is as follows:

- Lecithin is currently listed in FDA inactive ingredient (IIG) database at up to 15 mg/capsule for approved oral drug products and soybean-derived lecithin at up to 20 mg/capsule. The dose level of (b) (4) in PL2200 is (b) (4).  
The level of (b) (4) in PL2200 formulation is (b) (4) than amounts of lecithin currently used in approved drug products.
- However, lecithin is present in the human daily diet and is approved by FDA for human consumption as a direct food additive. Per monograph 21CFR 184 1400, lecithin is generally recognized as safe (GRAS) as a direct food substance.
- The NDA contains a comprehensive literature review on the toxicity of lecithins, and two supplemental toxicity studies with (b) (4).

Based on the above consideration in conjunction with a scientific literature review, there is no nonclinical concern related to the proposed use of lecithin under the condition specified in the proposed labeling in PL2200.

(2) The applicant has proposed separate specifications for monitoring the levels of free salicylic acid (SA) in the product during release (b) (4) and stability (b) (4).

The ONDQA review team considered the proposed stability specification for SA at (b) (4) is not consistent with the levels allowed for Aspirin USP tablets ( $\leq 3.0\%$ ) and USP Aspirin capsules ( $\leq 0.75\%$ ). The applicant responded on October 9, 2012 and proposed a specification limit of Not More Than (NMT) (b) (4) SA and NMT (b) (4) Total Related Substances. The stability specification level of SA at (u) (4) in PL2200 does not raise safety concerns from a nonclinical perspective.

- SA is a well-known active metabolite of aspirin and is responsible for the anti-inflammatory action of aspirin. It is also found in many approved salicylate drugs in the market (e.g., Pepto-Bismol). The SA limits defined in the USP monographs for Aspirin Tablets, Capsules, Coated Immediate-Release Tablets (PL2200 reference product), and Effervescent Tablets for Oral Solution are 0.3%, 0.75%, 3.0%, and 8.0%, respectively. The proposed specification of NMT (b) (4) is (b) (4) limit.

Overall, the stability specification level of SA at NMT (b) (4) in the PL2200 product does not raise any safety concerns from nonclinical perspective.

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\* For an adult at average body weight of 60kg

*There are no pharmacology/ toxicology issues identified for other excipients and impurities/degradants of the drug product.*

## 5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. See also discussion in section 13 regarding the clinical implications of the PK results.

The clinical pharmacology reviewer writes:

*The clinical program to support this application includes two clinical pharmacology studies, 1) bioequivalence study (PL-ASA-001) comparing Aspirin-PC versus Genuine Bayer aspirin in healthy volunteers, 2) food-effect study (PL-ASA-003) and a clinical 3) GI safety study (PL-ASA-002).*

*Sponsor has submitted in-vitro dissolution data to bridge the test formulation batch and two to-be-marketed formulation batches. The ONDQA/Biopharmaceutics reviewer, Dr. Tien Mien Chen has determined that the link is established between the test formulation and two to-be-marketed formulation batches based on mean dissolution profiles using in-vitro dissolution method.*

*The Office of Scientific Investigation audited study 001 and recommended the exclusion of 4 subjects and those subjects were excluded in the analyses below.*

### **Bioequivalence in fasting conditions:**

*The cross-over bioequivalence study (PL-ASA-001) was conducted between Aspirin-PC and reference drug Genuine Bayer® Aspirin tablets, in healthy volunteers at two dose levels, 325-mg and 650-mg (administered as two 325-mg tablets). Different group of subjects were recruited at each dose level.*

*The BE analysis for salicylic acid (the active moiety for pain) between Aspirin-PC and Bayer Aspirin® is shown in the Table below. The BE analysis was conducted with exclusion of subjects OSI has recommended (subjects 105, 126 in 325 mg group and 102 in 650 mg group). The results of the BE analysis showed that, Aspirin-PC meets the BE criteria for salicylic acid at 325-mg dose, but not at 650-mg dose (administered as two 325-mg tablets). At 325-mg dose level, the upper limit of 90% CI for log transformed salicylic acid  $C_{max}$   $AUC_{0-t}$ ,  $AUC_{0-inf}$  ratios for the test product to the reference product are within 80 to 125%. At 650-mg dose level, the lower limit of 90% CI for log transformed salicylic acid  $AUC_{0-t}$ ,  $AUC_{0-inf}$  ratios for the test product to the reference product is 75.8 and 78.0, respectively.*

**Table:** BE analysis for salicylic acid (the active moiety for pain) between Aspirin-PC and Bayer Aspirin®. The BE analysis was conducted with exclusion of subjects, which OSI has recommended.

Dose	Dependent	Geometric Mean Ratio	90% CI (Lower- Upper)
325 (n=12)	Cmax	105.7	93.0 - 120.2
325 (n=12)	AUC0-t	98.0	90.2 - 106.4
325 (n=12)	AUCinf	99.8	92.5 - 107.7
650 (n=14)	Cmax	101.3	89.0 - 115.2
650 (n=14)	AUC0-t	89.8	<b>75.8</b> - 106.4
650 (n=14)	AUCinf	91.3	<b>78.0</b> - 106.9

**Food Effect:**

The food effect on single dose Aspirin-PC was determined at 650-mg dose level (administered as two 325-mg capsules) using FDA recommended high fat food in the study PL-ASA-003. A total of 20 subjects were treated and all subjects completed both fasted and fed treatments. OSI has recommended exclusion of subjects 007 and 008 for food effect study. These two subjects were excluded in the food effect analysis. Administration of Aspirin-PC capsules with food resulted in a 6% lower AUC (AUC0-t and AUCinf) and a 22% lower Cmax for salicylic acid, respectively, and an approximately 1.64-hour delay in salicylic acid mean Tmax (4.58 hours vs 2.94 hours) compared to fasted conditions. The observed food effect for the Aspirin-PC product is not considered clinically significant and requires no dose adjustments.

Also, an approximately similar food effect of 18% lower salicylic acid Cmax and 1.6 hour delay in mean Tmax for immediate release aspirin was observed in the study by Koch et al. 1978 (Koch PA, Schultz CA, Wills RJ, Hallquist SL, Welling PG. 1978. Influence of food and fluid ingestion on aspirin bioavailability. *J Pharm Sci.* 1978; 67(11):1533-5). Therefore, the proposed product can be taken regardless of food.

During this drug's development program, the applicant was asked to assess the potential effects of lecithin on anti-platelet activity of aspirin. Study PL-ASA-001 evaluated pharmacodynamic (PD) effects. These PD data were reviewed by the clinical pharmacology team supporting the Division of Cardiology and Renal Products (DCRP). See Dr. Divya

Menon-Andersen's clinical pharmacology review and Dr. Thomas Marciniak's clinical review.

The clinical pharmacology reviewer writes:

*We recommend that a comparative description of the antiplatelet activity of aspirin not be presented in the label for PL2200 because the pharmacodynamic assays used (inhibition of serum thromboxane B2 and platelet aggregation) are not sensitive at doses evaluated in this study.*

Dr. Marciniak writes:

*We conclude that the antiplatelet effects of PL2200 appear equivalent to reference aspirin at the 325 mg dosage. In addition, pharmacokinetic equivalence is nearly achieved.* (b) (4)

I agree with these assessments. The slightly lower limit of the 90% CI for the 650 mg dose does not appear to be clinically relevant since this still provides a level of SA that falls within the therapeutic range of 1-2 tabs of aspirin. Additional sensitivity analyses including subjects that were dropped from these analyses described above, support the conclusions presented here. (b) (4)

## 6. Clinical Microbiology

Not applicable

## 7. Clinical/Statistical-Efficacy

Dr. Fang reviewed the literature provided by the applicant in their submission including three papers on antipyretic indication, seven papers on headache analgesia, two studies on pain relief with common cold, five studies for the treatment of dysmenorrhea, two in musculoskeletal pain, and nine in general pain conditions.

Dr. Fang writes:

*Due to the possibility of various types of limitations found in literature reports such as uncertainty about data quality, study conduct, and data analysis, and due to the lack of detailed information and the unavailability of original data, results reported in the literature*

*are generally not considered adequate support of efficacy in the absence of study reports containing the actual data. Nevertheless, the findings from the studies cited support the finding that aspirin works for treating aches and pains and/or fever in an OTC setting, based on the estimated effect size of treatment differences from pairwise comparisons between various aspirin doses and placebo, using time-specific PID measurements in multiple studies of fever, headache, sore throat, primary dysmenorrhea, and dental pain.*

### **Conclusion**

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

Therefore, it appears that sufficient information has been provided to support the use of aspirin as an anti-inflammatory and analgesic ingredient in this product and that the risk/benefit remains acceptable (see also section 8, below). (b) (4)

## **8. Safety**

There were no new safety concerns identified in this submission. As previously stated, aspirin has a long history of use and is present in a number of products. The safety profile is also well established. Dr. Hu, the medical reviewer, writes:

*The risk/benefit assessment notes that aspirin is included in the TFM for OTC internal analgesic products and has a well-established, favorable risk/benefit balance for short-term fever and pain relief. The risk of serious GI complications from aspirin use is well-documented. This review concludes that the safety and efficacy of PL2200 can still be bridged to safety and efficacy information from the aspirin literature and post-market experience from AERS. The pivotal BE trial did not demonstrate bioequivalence to monograph aspirin. Nevertheless, the deviations from BE (PL2200 325 mg is BE but PL2200 650 mg is slightly below BE) were unlikely to be clinically significant, and the available safety and efficacy information for aspirin are applicable to PL2200.*

*The Select Committee of GRAS Substances issued a 1979 evaluation of the safety of lecithin used in foods (see Section 9.1) which concluded that there is no evidence of a hazard from lecithin used at current levels. Patient exposure to the soy lecithin in each PL2200 capsule would be (b) (4) with a maximum daily exposure of (b) (4) which would be similar to the estimated natural dietary intake. It is concluded that there is no safety issue with the lecithin in PL2200.*

Dr. Shetty comments:

*Overall, data from different sources confirms known safety profile for aspirin. Even though this NDA is proposing a new formulation, there is no reason to believe that this new product will have a different safety profile than other nonprescription aspirin formulations.*

I agree with both assessments.

## **9. Advisory Committee Meeting**

Not applicable

## **10. Pediatrics**

The question for this NDA was whether the ASA-PC capsule triggers PREA based on the dosage form, because otherwise there was no new dosing regimen, population etc. After discussions with Scott Furness, Michael Jones, Melissa Furness, and Andrea Leonard-Segal, it was determined that this product was a capsule and even though liquid filled, was not a new dosage form, and therefore, did not trigger PREA. The conclusion was reached based on the following approach outlined by Michael Jones and explained by him as follows:

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



The applicant proposed to label the product for adults and children 12 years of age and older which is consistent with the TFM. I agree that this application does not trigger PREA.

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

## 12. Labeling

DMEPA has rejected several names including (b) (4). The reader is referred to the DMEPA review for a detailed discussion. As of this time the applicant has submitted labeling with the name Aspirin which is acceptable (discussed with and acceptable to DMEPA), and if desired, can request a name change after approval.

There were several additional comments from the DNRD labeling reviewer. I will not go into those in detail here except to mention 3 issues taken from the DNRD review as follows:

- 1) (b) (4)
- 2) *The phrases (b) (4) and (b) (4) are considered promotional language and may be misleading by implying a superiority claim (b) (4) and should be removed from the PDP.*
- 3) *Using the phrase (b) (4) on the PDP is not acceptable because it may imply (b) (4). The name (b) (4) is considered promotional. While some consumers may interpret the word (b) (4) in (b) (4) to imply an unknown benefit, most consumers would find the term meaningless. The phrase (b) (4) should be removed from the carton label.*

I agree with these comments.

(b) (5)

### 13. Decision/Action/Risk Benefit Assessment

Based on the above discussion, I recommend approval. There are no chemistry or toxicology issues that remain unresolved save for the final manufacturing inspection.

The clinical pharmacology studies demonstrate that this product is not bioequivalent to the chosen comparator (which is an aspirin product marketed under the monograph). However, the differences should not preclude approval based on the following discussion:

The results of the BE analysis (taking into account any subjects that needed to be excluded) showed that, Aspirin-PC meets the BE criteria for salicylic acid at 325-mg dose, but not at 650-mg dose (administered as two 325-mg tablets). At 325-mg dose level, the upper limit of 90% CI for log transformed salicylic acid  $C_{max}$   $AUC_{0-t}$ ,  $AUC_{0-inf}$  ratios for the test product to the reference product are within 80 to 125%. At 650-mg dose level, the lower limit of 90% CI for log transformed salicylic acid  $AUC_{0-t}$ ,  $AUC_{0-inf}$  ratios for the test product to the reference product is 75.8 and 78.0, respectively.

This still provides a dose of aspirin that falls within the therapeutic range (1-2 tabs). Therefore, consumers taking 2 capsules of ASA-PC will receive a potentially therapeutic dose. Even for the occasional user who has a slightly lower serum level of SA when using ASA-PC as compared to other marketed aspirin products, they can still benefit from this dose. A potential concern for early re-dosing in those taking ASA-PC has come up in internal discussions because of the slightly lower levels of SA. However, regular aspirin is not effective in all consumers and so already poses the possibility for early re-dosing in those individuals. This has not been considered a significant clinical concern with the use of aspirin specifically, or other OTC NSAID's, in general, and I do not believe is of clinical concern for ASA-PC.

Therefore, the data presented supports the safety and effectiveness of this aspirin product. There is no new information presented to alter the risk/benefit profile of aspirin, in general, and this aspirin-PC product, specifically.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOEL SCHIFFENBAUER  
01/14/2013