CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203697Orig1s000

CHEMISTRY REVIEW(S)

Memorandum to NDA 203697 File

From: Muthukumar Ramaswamy, Ph.D. (Chemistry Reviewer)

Date: January 8, 2013

Subject: Office of Compliance **Acceptable** Recommendation for the Facilities Associated With NDA 203697

Drug Product Name/Strength: TradeName (Aspirin) Capsules

Ref.: Previous CMC review dated 12/10/12 for NDA 22271 in DARRTS.

The Office of Compliance (OC) has determined that the relevant facilities employed for the manufacture and testing of the drug substances and the drug product (Aspirin capsules) are **Acceptable.** Therefore, from both CMC perspective and Office of Compliance point of view, this NDA (203697) is recommended for approval.

Attachment: Section of Establishment Evaluation Request Summary Report from OC indicating the Acceptable recommendation.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203697/000	**Sponsor:**	PLX PHARMA
Org. Code:	560		8285 EL RIO ST STE 130
Priority:	3		HOUSTON, TX 77054
Stamp Date:	14-MAR-2012	**Brand Name:**	PL2200 Aspirin Capsules, 325 mg
PDUFA Date:	14-JAN-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	15-NOV-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; CAPSULE, SOFT GELATIN LIQUID-FILLED; ASPIRIN; 325

FDA Contacts:	Y. LIU	Project Manager	3017961926
	M. RAMASWAMY	Review Chemist	3017961676
	S. DE	Team Leader	3017961664

Overall Recommendation:	ACCEPTABLE	on 08-JAN-2013	by T. SHARP	()	3017963208
	PENDING	on 20-DEC-2012	by EES_PROD		
	PENDING	on 19-DEC-2012	by EES_PROD		
	WITHHOLD	on 19-DEC-2012	by EES_PROD		
	PENDING	on 16-OCT-2012	by EES_PROD		
	PENDING	on 30-APR-2012	by EES_PROD		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-APR-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-DEC-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: (b) (4) **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-DEC-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 1124535 **FEI:** 1000513101
PHARMACEUTICS INTERNATIONAL INC
HUNT VALLEY, , UNITED STATES 210318213

DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-JAN-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-MAY-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-MAY-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

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

/s/

MUTHUKUMAR RAMASWAMY
01/08/2013

ALI H AL HAKIM
01/08/2013

NDA 203697

Acetylsalicylic acid capsules

PLx Pharma Inc.

Muthukumar Ramaswamy, Ph.D.

Division of Pre-Marketing Office of New Drug Quality Assessment

For the Division of Non-Prescription and Clinical Evaluation

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. NDA 203697

2. REVIEW: 2

3. REVIEW DATE: 12/10/2012

4. REVIEWER: Muthukumar Ramaswamy, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	3/12/2012
NDA Amendment	8/22/2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA Amendment	10/9/2012

7. NAME & ADDRESS OF APPLICANT:

Name: PLx Pharma Inc.

Address: 8285 El Rio, Suite 130, Houston, TX 77054

Representative: Jason Moore

Telephone: 713-842-3052

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To be proposed
b) Non-Proprietary Name (USAN): Aspirin
c) Code Name/# (ONDQA only): PL2200
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: For temporary relief of pain and fever.

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 325 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx X___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	7/25/12	Reviewed by M. Ramaswamy
	IV			1	Adequate	12/05/12	Reviewed by M. Ramaswamy.
	IV			1	Adequate	7/12/2004	Reviewed by R. Sood
	IV			1	Adequate	8/29/12	Reviewed by M. Ramaswamy. Component of an approved NDA 022512
	III			4	NA	NA	Component used in approved products ANDAs 040167, 040220, 040502 and 040516
	III			4	NA	NA	
	III			4	NA	NA	Component for an approved ANDA 074584, 077975, 078148
	III			4	NA	NA	ANDAs 040167, 040220, 040502, and 040516
	III			4	NA	NA	Container Component

(b) (4)		(b) (4)				for approved ANDAs 060359, 061904, 061905, and 062746
	III		4	NA	NA	Container Component for approved ANDAs 060359, 061904, 061905, and 062746
	III		4	NA	NA	Container Component for approved ANDA 070037
	III		4	NA	NA	Reviewed by Dr. Gene Holbert on 4/10/10. Container Component for approved ANDA 074937
	III		4	NA	NA	Component for approved ANDA 062421 and many NDAs
	IV		4	NA	NA	Part of recent approval for NDA 022370
	III		4	NA	NA	Part of recent approval for ANDA 201047

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	12/10/12	
Pharm/Tox	None		
Biopharm	Pending	TBD	Dr. Tien Mien Chen
LNC	(b) (4)	11/30/12	*In consultation with Dr. Joel Schiffenbauer / Mike Jones/Ali Al Hakim via email dated 11/30/12
EA	acceptable	Review date	Dr. Ramaswamy (Based on DMF Review dated 7/25/12)
Microbiology	none	NA	

(b) (4)

The Chemistry Review for NDA 203697

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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. For product packaged in HDPE bottles with desiccant or in blisters (b) (4) Storage temperature excursions are permitted up to 30°C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed drug product is a lipid suspension (b) (4) of aspirin filled in white opaque Size "00" (b) (4) capsule, printed in black with "ASA 325" on the body with a blue band. It contains 325 mg of Aspirin USP and is proposed for the temporary relief of minor aches and pains associated with colds, headaches, backaches, muscular aches, toothaches, premenstrual and menstrual cramps, minor pain of arthritis; and temporary reduction of fever.

The drug substance, Aspirin, USP (b) (4)) is manufactured by (b) (4) aspirin (b) (4) is a fine powder with a particle size specification of NLT (b) (4) retained on (b) (4). It does not exhibit any polymorphic form. (b) (4) . (b) (4) (b) (4). The Applicant has referenced DMF (b) (4) for all CMC information pertaining to the drug substance. The proposed specification for the drug substance meets the current U.S. Pharmacopeia monograph for aspirin.

The drug product formulation contains (b) (4) of soy lecithin (b) (4)), (b) (4) of medium chain triglycerides (b) (4) of anhydrous citric acid (b) (4) of colloidal silicon dioxide (b) (4) FD&C Blue #1, and pharmaceutical ink. (b) (4) hypromellose, carrageenan, potassium chloride, titanium dioxide. The drug product will be packaged in HDPE bottles as 30 and 120 capsules per bottle and in blisters as 7 count cold-form unit and 28 count (4 x 7 count) cold-form unit.

(b) (4) the composition of the formulation used in clinical formulations and the proposed commercial drug product are the same and the composition of (b) (4) used in commercial process is simple and acceptable.

Based on partitioning studies, the Applicant has claimed the use of lecithin [redacted] (b) (4) [redacted].

B. Description of How the Drug Product is Intended to be Used

The NDA recommends that the Trade Name capsules should be taken with a full glass of water with each dose. For adults and children 12 years and over may take 1 or 2 capsules every 4 hours or 3 capsules every 6 hours with a maximum of 12 capsules in 24 hours. For children under 12 years, the permitted dose will be per doctor's recommendation.

C. Basis for Approvability or Not-Approval Recommendation

From CMC perspective, the NDA is approvable pending acceptable recommendation from the Office of compliance.

Drug Substance: The applicant has referenced DMF [redacted] (b) (4) for CMC information pertaining to the drug substance, which is adequate to support the proposed application. The Applicant has referenced the following information in the DMF:

a) Data pertaining to the physical, chemical, structural characterization and stability data
b) Manufacturing site address, the method of manufacturing including controls used during manufacture and packaging; batch analysis information for API
c) Specifications necessary to ensure the identity, strength, quality, and purity of the drug substance including, analytical procedures, and acceptance criteria relating to stability, and potency

Drug Product: The NDA [redacted] (b) (4) describes adequately the chemistry, manufacturing, and control information for the proposed lipid suspension of aspirin filled in [redacted] (b) (4) capsules. [redacted] (b) (4) [redacted] The Applicant provided data to support the choice of each excipient and the levels of each excipient provided in the drug product.

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 [redacted] (b) (4) the expectation of USP monograph specification provided for soy lecithin. The application contains dimensions, drawing, and specification for key components used for packaging the drug product. The applicant provided extensive analytical data (that includes ^{31}P NMR and HPLC data) for the 5 lots of soy lecithin used in the manufacture of clinical and registration batches.

The levels of all components used in the PL2200 drug product [redacted] (b) (4) *the found in inactive ingredients database for oral products*. Soy lecithin is comprises [redacted] (b) (4) of the PL2200 capsule fill. Based on scientific literature review and the supplemental toxicity studies, the Applicant has determined that these levels of [redacted] (b) (4) [redacted] (b) (4) present in PL2200 aspirin capsules are safe (i.e., safety factor of [redacted] (b) (4) when daily consumption PL2200 aspirin capsules do not exceed 12 capsules per day. Soy lecithin is considered GRAS and is permitted as a food additive and therefore is acceptable.

The drug product is manufactured by Pharmaceutics International, Inc. (PII) at Hunt Valley, MD and packaged by [redacted] (b) (4) . The NDA contains adequate information on product development history and manufacturing procedure for the lipid suspension formulation filled in [redacted] (b) (4) capsules.

The manufacturing process for the drug product consists of [redacted] (b) (4)

The Applicant has proposed adequate in-process tests for the proposed process, [redacted] (b) (4)

The process evaluation section contains detailed information on the in-process controls used during the manufacture of registration batches which included [redacted] (b) (4) In addition, it contains development stability data to support the proposed bulk storage of [redacted] (b) (4) Bulk capsules will be stored in [redacted] (b) (4) per Kg of capsules.

The Applicant is proposing to use a batch size [redacted] (b) (4) for commercial operation, whereas the pivotal clinical batch were manufactured at [redacted] (b) (4) and is acceptable. Since the equipment used in manufacturing the operating principles, [redacted] (b) (4) fold scale up is acceptable. Prior to commercial manufacturing, the Applicant is planning to complete process validation studies, which is acceptable..

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 [redacted] (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 phospholipid content [redacted] (b) (4)

Per FDA request, the FDA has revised the specification for assay, % free and total salicylic acid, and total phospholipid content. The Applicant has proposed a total phospholipid content specification of [redacted] (b) (4) for release and a NLT [redacted] (b) (4) for shelf-life. The Applicant has also agreed to tighten the specification for Assay , % Free and Total salicylic acid content to [redacted] (b) (4), NMT [redacted] (b) (4), and NMT [redacted] (b) (4) respectively. The proposed specification for these quality attributes are consistent with batch analysis data for clinical and registration batches.

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 [redacted] (b) (4) In addition the Applicant also provided 12 months of real-time and intermediate stability data and 6 months of accelerated stability data for two (2) primary batches packaged in blister [redacted] (b) (4) [redacted] (b) (4) In general the 12-18 month real-time stability results for the primary batches remained within the recommended for % Label Claim, % free and total salicylic acid [redacted] (b) (4) and % dissolution.

An One-way analysis of real-time and intermediate storage stability data [redacted] (b) (4) *and thus indicating that storage under controlled temperature 15-25C/60% RH is necessary. Available stability data for all quality attributes also suggested that temperature excursions to 30°C are permitted for product packaged in bottles and blisters up to a period of 9 and 12 months respectively .*

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 (b) (4) *when stored under a controlled temperature 25 ± 2°C/60%RH.*

In proposing the above recommendation for blisters, the reviewer has taken into consideration the stability profile with the fact that the bulk product was held for a maximum period of 6 months at ambient temperature, prior to packaging in blisters (12 months real-time + 6 month bulk holding period)s.

The NDA provides batch history information for the drug product batches used in developmental, clinical and registration batches. It contains a copy of the executed batch production record with a description of the equipment, to be used for the manufacture of the drug product; the specification for each component, certificates of analysis for components and excipeints used for the manufacture of the drug product; It contains the name and address of the manufacturing facility or contract manufacturing facility involved in the manufacture, processing, packaging, or testing of the drug product and diluent as required by CFR 211.84(d). The NDA contains facility description for the drug product.

Manufacturing facilities. An acceptable recommendation from Office of Compliance for the manufacture's readiness to make this product is pending. The application contains a claim for categorical exclusion under CFR 25.31, which is acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Muthukumar Ramaswamy/Same date as draft review
Chemistry Branch Chief: Ali Al Hakim/ Same date as draft review

C. CC Block: Swapan De, CMC Lead, ONDQA

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

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/s/

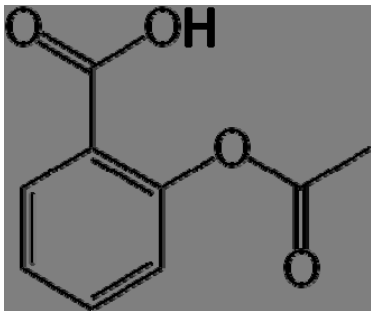
MUTHUKUMAR RAMASWAMY
12/10/2012

ALI H AL HAKIM
12/10/2012

Division of Nonprescription Clinical Evaluation

NDA:	**203,697**
Applicant:	PLx Pharma Inc. 8285 El Rio, Suite 130 Houston, TX 77054
Stamp Date:	03/14/2012
PDUFA Date:	01/14/2013
Proposed Proprietary Name:	(b) (4)
Established Name:	Aspirin
Dosage form and strength:	Capsule, liquid filled, 325 mg
Route of Administration:	Oral
Indications:	Temporarily relieve minor aches and pains associated with colds, headaches, backaches, muscular aches, toothaches, premenstrual and menstrual cramps, minor pain of arthritis; and temporarily reduce fever.
CMC Lead:	Swapan K De
ONDQA Fileability:	**Yes**

Name: Aspirin (2-acetyloxybenzoic acid)
Molecular formula: $C_9H_8O_4$
Molecular Weight: 180.157



Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Yes

Summary:

This is an e-CTD NDA application for PL2200 Aspirin Capsules (325 mg). Drug product PL2200 has been submitted as a 505(b)(2) NDA with reference to previously approved aspirin, 325 mg OTC product. PL2200 is an immediate release oral drug product consisting of aspirin, a non-steroidal anti-inflammatory drug, formulated in a lipid suspension of soybean-derived lecithin (b) (4) . Each capsule contains 325 mg of aspirin USP (active ingredient) and (b) (4) of soy lecithin.

Drug Substance:

Aspirin (2-acetyloxybenzoic acid) is an assembly of nine carbon atoms, four oxygen atoms and eight hydrogen atoms with a relative molecular mass 180.16 g/mol. Drug substance information is referred to a manufacturer's (b) (4) DMF (b) (4) entitiled (b) (4) A letter of authorization has been provided to access the drug substance manufacturer's DMF (b) (4)

Drug Product:
PL2200 Aspirin Capsules, 325 mg are an immediate-release two-piece (b) (4) (b) (4) capsule. Each capsule contains aspirin (b) (4) 325 mg, lecithin (b) (4) medium chain triglycerides (b) (4) anhydrous citric acid (b) (4) and colloidal silicon dioxide (b) (4) PL2200 capsules are packaged into 30-count 75 cc or 120-count 250 cc high density polyethylene (HDPE) bottles with desiccant canister and closed with an aluminum foil induction-sealed (b) (4) closure. PL2200 capsules are also packaged into 8-count (b) (4) foil blisters (b) (4)

The soy lecithin (b) (4) in PL2200 is composed of (b) (4) of the capsule fill and used as (b) (4) . (b) (4) Although soybean-derived lecithin is used in FDA approved drug products, such (b) (4) amount is not used in any approved drug product. The applicant has submitted justification and provided non-clinical study to

qualify the amounts of soy lecithin used in the drug product. It has been stated that the testing of microbial quality has been performed in this product due to presence of lecithin, a potential source of microbial contamination. Testing of microbial quality information should be reviewed by a microbiologist and a consult should be requested.

Release and stability specification for the drug product is included. It is noted that the related impurity of Aspirin includes Free Salicylic Acid (FSA), a major degradant of aspirin drug products which is formed via a hydrolytic degradation pathway of aspirin. Proposed acceptance criterion for FSA at release is (b) (4) and is deemed acceptable. However, proposed stability stability specification for FSA is NMT (b) (4) The proposed stability specification of FSA (b) (4) is (b) (4) than the FSA in reference Aspirin Products (b) (4). Thus, the impurities might needs to be qualified and Pharm/tox review might be needed for this issue.

Proposed Drug Product (PL2200 Aspirin Capsules, 325 mg) Release Specification:

Tests	Analytical Procedure	Acceptance Criteria
Appearance	GTM 04-0072 (Visual)	(b) (4)
Identification	TM 07-234	
	TM 07-234	
Assay of Aspirin (HPLC)	TM 07-234	
Related Compounds (HPLC) Salicylic Acid (SA) Other Related Substances Total Related Substances	TM 07-234	
Lecithin (HPLC) (b) (4)	(b) (4) SOP # 200151 (b) (4)	
Dissolution – (b) (4) Stage 1 (Test 6 units)	TM 07-0233; Current USP <711>	
Stage 2 (Test additional 6 units)	TM 07-0233; Current USP <711>	
Stage 3 (Test additional 12 units)	TM 07-0233; Current USP <711>	
Uniformity of Dosage Units by Content Uniformity	TM 07-0234 Current USP <905>	

Microbial Enumeration Total Aerobic Bacteria Total Combined Mold & Yeast	Current USP <61>	(b) (4)
Test for Specified Microorganisms *Salmonella* *Escherichia coli* *Staphylococcus aureus* *Pseudomonas aeruginosa*	Current USP <62>	

Abbreviations: GTM, general test method, NMT, no more than, NLT, not less than.
[1] Developmental specification was Q o(b) (4) The proposed specification was tightened based on stability data, dissolution profile and IVIVC.

PL2200 Aspirin Capsules, 325 mg Stability Specification:

Tests	Analytical Procedure (Technique)	Acceptance Criteria
Appearance	GTM 04-0072[1]	(b) (4)
Assay of Aspirin (HPLC)	TM 07-0234	
Related Compounds (HPLC) Salicylic Acid (SA) Unspecified Degradants Total Degradants	TM 07-0234	
Lecithin (HPLC) (b) (4)	(b) (4) SOP 200151	
(b) (4)		
Dissolution -- (b) (4) Stage 1 (Test 6 units) Stage 2 (Test additional 6 units) Stage 3 (Test additional 12 units)	TM 07-0233 Current USP <711> TM 07-0233 Current USP <711> TM 07-0233 Current USP <711>	
Microbial Enumeration Total Aerobic Bacteria Count Total Combined Mold & Yeast Count	Current USP <61>	
Test for Specified Microorganisms *Salmonella* *Escherichia coli* *Staphylococcus aureus* *Pseudomonas aeruginosa*	Current USP <62>	

[1]GTM = general test method, [2]NMT = no more than

12-month stability data for three primary batches and up to 36-month supportive stability data have been provided at long term conditions (25°C/60% RH) of the drug product in the proposed bottle (30 count/75 cc HDPE/2 g silica and 120 count/250 cc HDPE/6 g silica). The applicant has requested (b) (4) shelf-life of the drug product. Similarly, 12-month stability data for one batch and 6-month stability data for two batches are provided for the drug product in the blister (8 count aluminum blister) packaging configuration and the applicant has requested (b) (4) shelf life of the drug product. In both cases (bottle and blister) 6-month stability data at accelerated conditions (40°C/75% RH) are included.

Critical Issues:

Drug substance:

- DMF (b) (4) should remain adequate to support the NDA 203-697. It should contain manufacturing process details with appropriate critical process parameters, specifications with impurity profile for the drug substance and stability data to support a retest period. (b) (4) drug substance particle size acceptance criterion should be included in the specifications.

Drug Product:

- There is detailed formulation development section in 3.2P which should be evaluated in-depth.
- Are the components of (b) (4) adequately characterized and controlled in the drug product?
- (b) (4)
- (b) (4)

- Free Salicylic Acid (FSA) is the major degradant present in aspirin drug products which is formed via a hydrolytic degradation pathway of aspirin. Proposed acceptance criterion for FSA at release is (b) (4) and is deemed acceptable. However, proposed stability stability specification for FSA is (b) (4) Is it acceptable considering reference listed Aspirin Drug product has FSA limits of (b) (4)
- Has adequate justification been provided for the microbial limits test in the release specification of the drug product? Microbiological Attributes section 3.2.P.2.5 is included and needs a consult review by a microbiologist.
- In vitro dissolution method for PL2200 Aspirin capsules is significantly different from the immediate release profile of other aspirin products. The proposed method (b) (4) . The method is described with justification and should be consulted to the Biopharmaceutics team in ONDQA.
- Is the submitted 12-month stability data for three batches of drug product is enough to support the proposed (b) (4) shelf-life of the drug product in bottle (30 count/75 cc HDPE/2 g silica and 120 count/250 cc HDPE/6 g silica)?
- Is the submitted 12-month stability data for three primary batches and up to 36-month supportive stability data are adequate to support the proposed (b) (4) shelf-life of the drug product in the proposed bottle (30 count/75 cc HDPE/2 g silica and 120 count/250 cc HDPE/6 g silica)?
- Is the submitted 12-month stability data for one batch and 6-month stability data for two batches are adequate to support the proposed (b) (4) shelf life of the drug product in the blister (8 count aluminum blister) packaging configuration?

Comments and Recommendations:

The application is fileable. Submitted manufacturing facilities have been entered into the EES. The reviewer should confirm the accuracy and completeness of the EES entries. This NDA does not qualify as a QbD submission based on the criteria in the ONDQA interim policy (no design space, PAT, RTRT, reduced end-product testing etc.).

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: #203,697 **NDA Type: 505 (b)(2)** **Established/Proper Name:** Aspirin

Applicant:
PLx Pharrma Inc. **Letter Date: 03/12/2012**

Stamp Date: 03/12/2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		Looks to be in standard eCTD format.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		Appears to be
3.	Are all the pages in the CMC section legible?	X		Appears to be
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Appears to be

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Six facilities identified, all have complete addresses and FEI Numbers.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Appears to be
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Appears to be

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Appears to be.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Appears to be

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		X	(b) (4) [redacted]
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	
14.	Does the section contain information regarding the characterization of the DS?		X	
15.	Does the section contain controls for the DS?		X	
16.	Has stability data and analysis been provided for the drug substance?		X	
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Appears to be
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		Appears to be
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Pharmaceutical development section has adequate information.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		Appears to be
25.	Does the section contain controls of the final drug product?			Appears to be
26.	Has stability data and analysis been provided to support the requested expiration date?			Data have been included and needs to be evaluated
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		X	Needs to be requested based on reviewers judgment.

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		Microbiological Attributes section 3.2.P.2.5 is included and needs to be reviewed by a microbiologist.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Appears to be

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
34.	Does the application contain dissolution data?	X		
35.	Is the dissolution test part of the DP specifications?	X		
36.	Does the application contain the dissolution method development report?	X		
37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?		X	

39.	Does the application include a IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is there any in *vivo* BA or BE information in the submission?	X		

K. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
42.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	
44.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		It would depend on initial review by the reviewer.

{See appended electronic signature page}

Swapan K De
CMC Lead
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim
Branch Chief
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

Manufacturer(s) of PL2200 Aspirin Capsules, 325 mg

Drug Substance [Aspirin (2-acetyloxybenzoic acid)] Manufacturer:

(b) (4)

Drug Product (PL2200 Aspirin Capsules) Manufacturer:

Drug Product Manufacturer:
Pharmaceutics International, Inc. (PII)
10819 Gilroy Road
Hunt Valley, MD 21031
Tel. 410-584-0001
Fax. 410-584-0007
www.pharm-int.com
FEI# 1000513101
PII Contact Person: Alex McClung, Sr. Director Quality Assurance, Corporate Compliance
Tel. 410-584-0001, extension 1270
Fax. 410-584-0007
Email: AMcClung@pharm-int.com
24-Hour PII Contact Person: Khurshaid Kazmi, Vice President Operations & Administration
Tel. (b) (6) (cell)

Drug Product Release and stability testing:

(b) (4)

(b) (4)

(b) (4)

Drug product release testing (Lecithin testing)

(b) (4)

Packaging facilities:

(b) (4)

(b) (4)

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/s/

SWAPAN K DE
05/02/2012

ALI H AL HAKIM
05/02/2012