# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203697Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# ONDQA BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA#**: | 203697/N-000 |
| **Submission Date:** | 03/14/12 and 11/13/12 |
| **Brand Name:** | PL2200 |
| **Generic Name**: | Aspirin |
| **Formulation:** | Immediate release (IR) oral capsule |
| **Strength**: | 325 mg (One strength) |
| **Applicant**: | PLx Pharma Inc. (PLx) |
| **Type of submission:** | Original NDA (standard) |
| **Reviewer**: | Tien-Mien Chen, Ph.D. |

## SYNOPSIS

### *Background*

Aspirin (acetylsalicylic acid) has been known as a pain reliever and a fever reducer. Various aspirin OTC (over the counter) products are currently on the market. PL2200, aspirin (acetylsalicylic acid) capsule of 325 mg, was developed under IND 74,290. It is a liquid-filled IR capsule containing a lipidic suspension of aspirin for oral administration. PL2200, Aspirin Capsule 325 mg, is an IR two-piece (b) (4) capsule containing a lipidic suspension of 325 mg aspirin for oral administration. Lecithin as a (b) (4), is an excipient functioning as an (b) (4)

### *Current Submission*

On 03/12/12, PLx Pharma Inc. (PLx) submitted Original NDA 203697 for PL2200, aspirin (acetylsalicylic acid) capsule 325 mg under 505(b)(2) referencing to RLD (reference listed drug), Genuine Bayer's Aspirin tablet, 325mg. PLx Pharma is seeking the following OTC indications for PL2200:

- Temporarily relieve minor aches and pains associated with Colds, Headaches, Backaches, Muscular aches, Toothaches, Premenstrual and menstrual cramps, Minor pain of arthritis,
- Temporarily reduce fever.

The NDA submission included:

- A bioequivalence (BE) study (No. **PL-ASA-001**) comparing PL2200 to the RLD product, Genuine Bayer® Aspirin tablets, 325mg. It relies on FDA's prior findings of safety and efficacy of aspirin as well as supportive literature references.
- A food-effect bioavailability pharmacokinetic (PK) study (No. **PL-ASA-003**).

- The toxicology study results for [redacted] (b) (4), a lecithin excipient in PL2200 exciding the IIG limit for lecithin in an orally administered drug product, when PL2200 is administered at the maximum permitted label dosage.
- The CMC information.
- The dissolution development report, proposed dissolution method and acceptance criterion, and some information on a proposed *in vivo-in vitro* correlation (IVIVC) model submitted to support the selection of the proposed dissolution method and acceptance criterion.

***Biopharmaceutics Review***

The Biopharmaceutics review is focused on the evaluation and acceptability of: **1)** the proposed dissolution method and acceptance criteria, and **2)** the comparative dissolution profile data bridging the clinical and to-be-marketed (TBM) formulations. The TBM and the clinically tested formulations have identical components except for additional printing on the surface of the finished TBM product.

***Reviewer Comments:***

1. The proposed dissolution method based on the release of total salicylates is acceptable. The Applicant's revised proposal of Q= [redacted] (b) (4) at 30 min using 150 rpm is also acceptable. Therefore, the following dissolution method and acceptance criterion for PL2200 (aspirin) capsule, 325 mg should be implemented.

   **USP Apparatus: II (Paddle)**
   **Speed: 150 rpm**
   **Medium: 0.05M Sodium Bicarbonate buffer/0.02M Cholic Acid /1% Pancreatin (final pH 7.0±0.1)**
   **Acceptance Criterion: Q= [redacted] (b) (4) at 30 min**

2. The dissolution profile data comparing the clinically tested formulation (without printing) and the TBM (to-be-marketed) formulation with printing on the drug product support the bridging of these products.

3. The submitted IVIVC information did not meet the IVIVC requirement per SUPAC guidance. Therefore, the IVIVC information included in the report (No. **CAR-PL2200-004**) was briefly reviewed; however, the results were not used to support the proposed acceptance criterion.

4. On 12/07/12, FDA informed the Applicant that their revised proposal of Q= [redacted] (b) (4) at 30 min using 150 rpm for the dissolution acceptance criterion was acceptable and FDA requested the submission of an updated specifications table for the drug product including the revised dissolution acceptance criterion.

**RECOMMENDATION**

The Biopharmaceutics team has reviewed the information included in NDA 203-697. From the Biopharmaceutics perspective NDA 203-697 for PL2200, aspirin (acetylsalicylic acid) capsule is recommended for approval.

_____ 12/02/12

Tien-Mien Chen, Ph.D. Date
ONDQA Biopharmaceutics Reviewer

_____ 12/09/12

Angelica Dorantes, Ph.D. Date
ONDQA Biopharmaceutics Team Leader

CC: DARRTS/NDA 203697/RLostritto

# PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

## BACKGROUND

Aspirin (acetylsalicylic acid) has been known as a pain reliever and a fever reducer. Various aspirin OTC (over the counter) products are currently on the market. PL2200 aspirin (acetylsalicylic acid) capsules of 325 mg was developed under IND 74,290. It is a liquid-filled IR capsule containing a lipidic suspension of aspirin for oral administration.

The lecithin excipient [redacted] (b) (4) used in the drug product [redacted] (b) (4) the approved amount listed in the FDA inactive ingredients guide (IIG) for an orally administered drug product. PLx has received extensive development feedback from various FDA divisions and has sought to comply with each requirement or commitment.

## CURRENT SUBMISSION

On 03/12/12, PLx Pharma Inc. (PLx) submitted an original NDA203697 for PL2200, aspirin (acetylsalicylic acid) capsules 325 mg under 505(b)(2) referencing to RLD (reference list drug), Genuine Bayer's Aspirin tablets, 325mg. PLx Pharma is seeking the following OTC indications for PL2200:

- Temporarily relieve minor aches and pains associated with
  Colds, Headaches, Backaches, Muscular aches, Toothaches, Premenstrual and menstrual cramps, Minor pain of arthritis,
- Temporarily reduce fever.

The NDA submission included:

- A bioequivalence (BE) study (No. **PL-ASA-001**) comparing PL2200 to RLD product, Genuine Bayer® Aspirin tablets, 325mg, a product marketed under the TFM, and relies on FDA's prior findings of safety and efficacy of aspirin set forth in that TFM as well as supportive literature references.
- A food-effect bioavailability pharmacokinetic (PK) study (No. **PL-ASA-003**).
- The toxicology study results for [redacted] (b) (4), a lecithin excipient in PL2200 that [redacted] (b) (4) the IIG limit for lecithin in an orally administered drug product when PL2200 is administered at the maximum permitted label dosage.
- The CMC information.
- Dissolution development report, proposed dissolution method, dissolution acceptance criterion, and some information on the *in vivo-in vitro* correlation to support the selection of the proposed dissolution method and acceptance criterion.

The BE studies are to be reviewed by the Office of Clinical Pharmacology (OCP). The CMC information is to be reviewed by the chemist/ONDQA and the dissolution development report, proposed dissolution method and the acceptance criterion will be reviewed by the Biopharmaceutics/ONDQA.

## BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of: 1) the proposed dissolution method and acceptance criterion, and 2) comparative dissolution profile data bridging the clinical and TBM formulations. The TBM and the clinically tested formulations have identical components except for additional printing on the surface of the finished TBM product.

## FORMULATION COMPARISONS

PL2200 Aspirin Capsule, 325 mg, is an IR two-piece [redacted] capsule containing a lipidic suspension of 325 mg of aspirin for oral administration. The composition/formulation is shown below.

**Table 1. The Composition/Formulation of the TBM PL2200 (Aspirin) IR 325 mg Capsules**

| Ingredient | Function | mg/capsule | Quality Standard |
|---|---|---|---|
| [redacted] | | | |
| Aspirin [redacted] | Active Ingredient | 325.0 | USP |
| Lecithin [redacted] | [redacted] | [redacted] | DMF (3) |
| Medium Chain Triglycerides | | | NF |
| Anhydrous Citric Acid | | | USP |
| Colloidal Silicon Dioxide | | | NF |
| [redacted] | | | |
| [redacted] | | | DMF (3) |
| [redacted] | | | |
| [redacted] | | | USP |
| FD&C Blue #1 | [redacted] | | FDA/EC |
| [redacted] | | N/A | USP |
| [redacted] | | N/A | USP |
| **Total Weight** | | **881.6** | |

Lecithin as a [redacted], is an excipient functioning as an [redacted]

**Note**: Soy lecithin comprises [redacted] of the PL2200 capsule fill, which [redacted] 1). FDA limits as an inactive ingredient (IIG) for oral route of administration, at oral

dose amounts of up to 20 mg/soft gelatin capsule and up to 0.2% in oral suspensions and 2). FDA limits as an IIG in approved drug products, at oral dose amounts of up to 15 mg/capsule, 53 mg/chewable bar, and as an oral powder for suspension at 3.34%.

Minor changes have been made to the PL2200 drug products since the performance of the BE study (No. **PL-ASA-001**). [redacted] A comparison in dissolution profiles between the clinically tested and the TBM formulations was submitted and reviewed here.

**DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION**

Aspirin showed poor solubility at acidic pH (high stability), but the solubility is increased significantly at alkaline pH (rapid degradation). PL2200 intends to have Stability [redacted] salicylic acid). The absorption of orally administered aspirin is known to be dissolution limited and pH dependent as shown below.

**Figure 1. pH-Dependent Solubility and Hydrolysis of Aspirin**

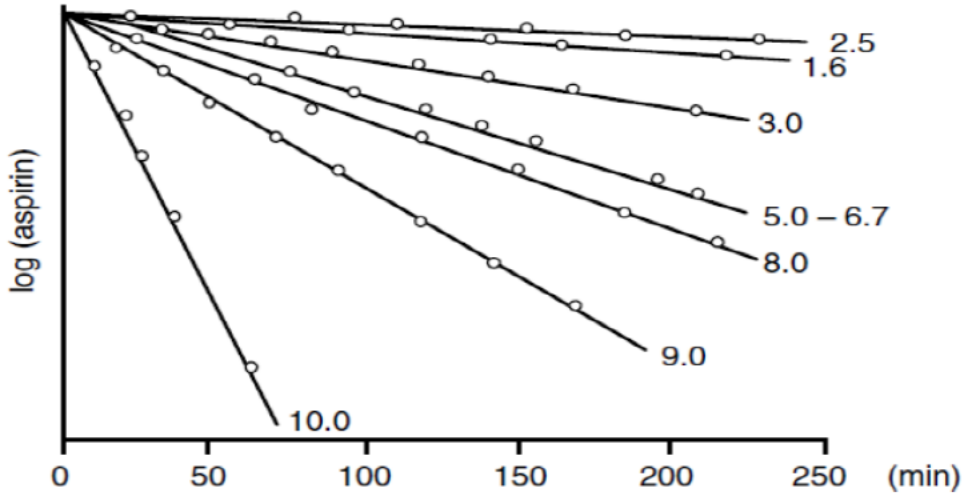


**Table 2. Aspirin Solubility over Biorelevant pH Values at Room Temperature**

| pH | 2.5 | 3.5 | 4.5 | 5.5 | 6.5 | 7.5 |
|---|---|---|---|---|---|---|
| Test | Concentration mg/mL (Average ± Standard deviation)* | | | | | |
| Drug Substance (Aspirin) | | | | | | |
| Aspirin | 3.70 ± 0.08 | 3.89 ± 0.11 | 3.89 ± 0.17 | 3.94 ± 0.09 | 5.02 ± 0.08 | 7.41 ± 0.13 |
| Salicylic acid | 0.36 ± 0.01 | 0.57 ± 0.02 | 0.64 ± 0.03 | 0.71 ± 0.01 | 1.42 ± 0.02 | 2.96 ± 0.06 |
| Total salicylates | 4.16 ± 0.09 | 4.64 ± 0.14 | 4.73 ± 0.21 | 4.87 ± 0.11 | 6.87 ± 0.11 | 11.27 ± 0.20 |

* Results are presented as average ± standard deviation of triplicate measurements (n=3). Buffer: 50 mM Phosphate-Citrate. [redacted] = Lot FRH0727508.

PL2200 (Aspirin) formulation is lipid-based, so the "USP Compendial Dissolution Method" won't work. The *in vitro* release of the API (active pharmaceutical ingredient) from PL2200 in compendial aspirin media (acetate buffer, pH 4.5) and a simulated jejunal fluid (phosphate buffer, pH 7.4) was less than (b) (4) of label claim over 2 hours, and no more than (b) (4)% was released at high agitation at infinity ( (b) (4) .

**Dissolution Method Development**

The release of aspirin in various conditions was tested and is summarized below.

(b) (4)

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(b) (4)

***Reviewer's Comment:***
*The Applicant's proposal and the rationale for using % release of total salicylates for dissolution testing are acceptable.*

**Proposed Dissolution Method No. TM-07-0233**
As expected for lipid-based formulations such as PL2200, complete release of aspirin from PL2200 capsules required lipid emulsification with a bile acid and digestion of the lipid with enzymes.

Dissolution conditions specify a USP Type II apparatus (paddle), 0.05M Sodium Bicarbonate buffer with 20 mM Cholic Acid (CA) and 1% Pancreatin Enzyme (E) at a final pH 7.0, 37°C, in a final volume of 900 ml, and a paddle speed of 150 rpm (**TM-07-0233**). The dissolution development is summarized below.

**I. Effect of pHs and Rotational Speeds on Total Salicylates Released**
The release of total salicylates was tested with different pHs and paddle rational speeds as shown below.

(b) (4)

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The Applicant concluded that the 150 rpm dissolution method (**TM-07-0233**) may be the stability indication discriminatory method. Therefore, routine use of the test method **TM-07-0233** (150 rpm) in commercial production is planned.

The proposed Dissolution Method and acceptance criterion are shown below.

| | |
|---|---|
| **USP Apparatus:** | **II (Paddle)** |
| **Speed:** | **150 rpm** |
| **Medium:** | **0.05M Sodium Bicarbonate buffer/0.02M Cholic Acid /1% Pancreatin (final pH 7.0±0.1)** |
| **Acceptance Criterion:** | **Q=** (b) (4) **at** (b) (4) |

After reviewing the proposed dissolution method and the available dissolution data, the proposed dissolution medium is considered acceptable, but NOT the dissolution paddle speed (150 rpm) or the acceptance criterion (Q= (b) (4) at (b) (4)). An information request was sent to the Applicant on 09/19/12 requesting the revision to the dissolution paddle speed and the acceptance criterion as follows.

Agency's proposal in the 09/19/12 letter:

**Change from the proposed dissolution paddle speed of 150 rpm & Q=** (b) (4) **at** (b) (4)
**To the Agency's proposed dissolution paddle speed of** (b) (4) **& Q=** (b) (4) **at 30 min**

The Applicant responded on 11/13/12 and counter-proposed an alternative acceptance criterion of Q=(b) (4) at 30 min, but using the same medium with a paddle rational speed of 150 rpm. Additional analyses were conducted on three stability batches (Nos. 13105.003, 13105.004, and 13105.005), a clinically tested biobatch No. 131105.001, and a TBM product batch (No. 13105.006). Please see mean and individual dissolution data in Appendix for details.

The rationale/justification for the newly proposed acceptance criterion is summarized below.

(b) (4)

**Table 5. Dissolution Failure at 150 RPM**

| Dissolution Time (min) | PL2200 Lot | Age of PL2200 Aspirin Capsule at Dissolution "Failure" (months) by Package Configuration (b) (4) | | | |
|---|---|---|---|---|---|
| 30 | 13105.001 | 6 months | NA | NA | NA |
| | 13105.003 | NA | none[b] | none | none |
| | 13105.004 | NA | none | none | none |
| | 13105.005 | NA | none | none | none |
| | 13105.006 | NA | NA | NA | none |
| (b) (4) | 13105.001 | none | NA | NA | NA |
| | 13105.003 | NA | none | none | none |
| | 13105.004 | NA | none | none | none |
| | 13105.005 | NA | none | none | none |
| | 13105.006 | NA | NA | NA | none |
| | 13105.001 | none | NA | NA | NA |
| | 13105.003 | NA | none | none | none |
| | 13105.004 | NA | none | none | none |
| | 13105.005 | NA | none | none | none |
| | 13105.006 | NA | NA | NA | none |

[a] "Failure" means the minimum dissolution test result for a capsule in that particular lot and Package Configuration is less than (b) (4)

[b] "None" means "No Failures"; the minimum dissolution test result for a capsule in that particular lot and Package Configuration is always greater than (b) (4)

NA=not applicable

**Table 6. Dissolution Failure by Paddle Rotational Speed**

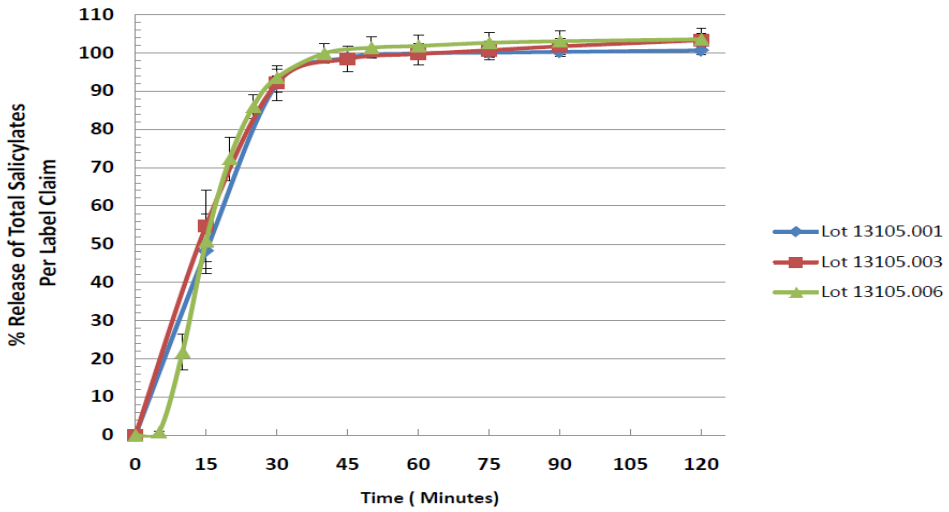
| Dissolution Test Paddle Speed | Total Number of Lots/Packaging Configurations Tested | PL2200 Lots/Packaging Configurations Classified as Dissolution "Failures" at Q of (b) (4) | | (b) (4) |
|---|---|---|---|---|
| | | 30 minutes | | |
| | | n | % | |
| (b) (4) | 10 | 5 | 50 | |
| 150 RPM | 11 | 1 | 9 | |

***Reviewer's Comment:***
*The above newly proposed acceptance criterion (Q= (b) (4) at 30 min using 150 rpm) with supporting data (less failure rate) and the rationale/justification were reviewed and found acceptable.*

Clinically Tested vs. To-Be-Marketed (TBM) Formulation Comparisons:
As discussed in the 12/16/11 Pre-NDA meeting (under IND 74,290), Q# 7 on the similarity of the above two formulations, the Applicant stated that the TBM formulation would have additional printing on the surface of the finished product ( (b) (4) ), all other components are identical. Per request by the Clinical pharmacology reviewer, a link between these two formulations was examined.

The Applicant did provide the comparative dissolution profile data. The complete release profiles of 3 batches of PL2200 are illustrated below. Lot No. 13105.001 was used in the pivotal bioequivalence study **PL-ASA-001**, and lot 13105.003, a primary stability batch, was also used in the food effect pharmacokinetics study **PL-ASA-003**. The TBM product is represented by lot No. 13105.006. Please see mean and individual dissolution data in Appendix for details.

**Figure 13. Comparison of Release Profiles of PL2200 Aspirin Capsules, 325 mg for Clinically Tested and the TBM Formulations (n=12 caps/batch)**




***Reviewer's Comment:***

*The results showed comparable dissolution profiles among the above three batches indicating similarity of these batches. The results support the bridge between the clinically tested and the TBM formulations, based on the release of total salicylates.*

***Overall Comments:***

- *The submitted dissolution development report and proposed dissolution method based on the release of total salicylates are found acceptable.*
- *The Applicant revised dissolution acceptance criterion (Q=* (b) (4) *at 30 min using 150 rpm) and the rationale/justification were reviewed and found acceptable.*
- *The provided dissolution profile comparison data for the clinically tested formulation (without printing) and the TBM formulation with a printing on the drug product are also found acceptable.*
- *The submitted IVIVC information did not meet the IVIVC requirements per SUPAC guidance. Therefore, the submitted IVIVC information included in the report (No.* ***CAR-PL2200-004****) was briefly reviewed; however, the results were not used to support the selection of the proposed dissolution method and acceptance criterion.*

# NDA 203697/N-000 for
# PL2200 Aspirin (Acetylsalicylic acid)

# Appendix

# Mean and Individual Dissolution Data of Three Primary Stability Batches and Two Biobatches

**Table 1. Release of Aspirin in Simulated Intestinal Fluid supplemented with Bile Acid and Enzymes for the Retained Primary Stability Sample Lot No. 13105.003A (150 rpm) Base on Total Salicylates**

**Dissolution Medium:** 0.05M Sodium Bicarbonate Buffer, 0.02M Cholic Acid, 1% Pancreatin, pH 7.0
**Dissolution Apparatus:** Apparatus II
**Speed:** 150 rpm
**Component Name:** **Total Salicylates**

| | Time (min) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Vessel** | **15** | **30** | **45** | **60** | **75** | **90** | **120** | **Inf** |
| 1 | (b) (4) | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | | | | | | | | |
| 10 | | | | | | | | |
| 11 | | | | | | | | |
| 12 | | | | | | | | |
| **Mean** (n=12) | 54.8 | 92.1 | 98.4 | 99.7 | 100.7 | 101.7 | 103.3 | 103.9 |
| **%RSD** | 17.2 | 4.9 | 3.4 | 2.8 | 2.4 | 2.1 | 1.7 | 1.7 |

Reference: Notebook 2250, pp. 136,137 (Vessels 1-6), pp. 144, 145 (Vessels 7-12)

**Table 2. Release of Aspirin in Simulated Intestinal Fluid supplemented with Bile Acid and Enzymes for the Retained Primary Stability Sample Lot No. 13105.004A (150 rpm) Base on Total Salicylates**

**Dissolution Medium:** 0.05M Sodium Bicarbonate Buffer, 0.02M Cholic Acid, 1% Pancreatin, pH 7.0)
**Dissolution Apparatus:** Apparatus II
**Speed:** 150 rpm
**Component Name:** **Total Salicylates**

| | Time (min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Vessel** | **7.5** | **15** | **30** | **45** | **60** | **75** | **90** | **120** | **Inf** |
| 1 | (b) (4) | | | | | | | | |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| **Mean** (n=12) | 8.5 | 56.1 | 95.6 | 100.1 | 101.2 | 102.5 | 103.3 | 104.3 | 104.6 |
| **%RSD** | 44.0 | 16.3 | 3.3 | 2.3 | 1.8 | 1.5 | 1.2 | 1.1 | 1.0 |

Reference: Notebook 2250, pp. 171, 172

**Table 3. Release of Aspirin in Simulated Intestinal Fluid supplemented with Bile Acid and Enzymes for the Retained Primary Stability Sample Lot No. 13105.005A (150 rpm) Base on Total Salicylates**

**Dissolution Medium:** 0.05M Sodium Bicarbonate Buffer, 0.02M Cholic Acid, 1% Pancreatin, pH 7.0
**Dissolution Apparatus:** Apparatus II
**Speed:** 150 rpm
**Component Name:** **Total Salicylates**

| | Time (min) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Vessel** | **7.5** | **15** | **22.5** | **30** | **45** | **6** | **75** | **90** | **120** | **Inf** |
| 1 | (b) (4) | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
| 7 | | | | | | | | | | |
| 8 | | | | | | | | | | |
| 9 | | | | | | | | | | |
| 10 | | | | | | | | | | |
| 11 | | | | | | | | | | |
| 12 | | | | | | | | | | |
| **Mean** (n=12) | 5.9 | 55.1 | 84.5 | 96.8 | 102.8 | 103.4 | 104.3 | 104.5 | 104.9 | 105.1 |
| **%RSD** | 51.7 | 8.6 | 3.1 | 1.4 | 1.2 | 0.8 | 0.9 | 0.8 | 0.9 | 0.8 |

Reference: Notebook 2758, pp. 9, 12

**Table 4. Complete Dissolution Profiles of PL2200 Drug Product used in Pivotal BE Study (Biobatch No. 13105.001B)**

**PL2200 Lot Number:** **13105.001B, Initial**
**Speed:** 150 rpm
**Component Name:** Total Salicylates

| | Time (mins) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Vessel** | **15** | **30** | **45** | **60** | **75** | **90** | **120** | **135** |
| 1 | (b) (4) | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | | | | | | | | |
| 8 | | | | | | | | |
| 9 | | | | | | | | |
| 10 | | | | | | | | |
| 11 | | | | | | | | |
| 12 | | | | | | | | |
| **Mean** (n=12) | 48.2 | 91.9 | 98.8 | 99.9 | 100.1 | 100.3 | 100.7 | 100.7 |
| **SD** | 6.0 | 2.1 | 1.0 | 1.0 | 1.2 | 1.1 | 1.1 | 1.1 |
| **%RSD** | 12.5 | 2.3 | 1.0 | 1.0 | 1.2 | 1.1 | 1.1 | 1.1 |

Reference: Notebook 1738, p. 110 for Vessels 1-6; Notebook 1738, p. 114 for Vessels 7-12.
Notes: Two sets of samples from lot 13105.001 were tested, using TM-07-0233.

- Vessels 1-6 contain PL2200 from lot 13105.001 batch release, which is the bulk release. The capsules were packaged in HDPE bottles, which were designated 13105.001B 1 month 25°/60%RH.
- Vessels 7-12 contain PL2200 from lot 13105.001B, and 1 month 25°/60%RH. data are reported.

**Table 5. Complete Dissolution Profile of PL2200 Drug Product used in Pivotal Food Effect Study (Biobatch No. 13105.003A)**

**PL2200 Lot Number:** **13105.003A, Initial**
**Speed:** 150 rpm
**Component Name:** Total Salicylates

| | Time (mins) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Vessel** | **15** | **30** | **45** | **60** | **75** | **90** | **120** |
| 1 | (b) (4) | | | | | | |
| 2 | | | | | | | |
| 3 | | | | | | | |
| 4 | | | | | | | |
| 5 | | | | | | | |
| 6 | | | | | | | |
| 7 | | | | | | | |
| 8 | | | | | | | |
| 9 | | | | | | | |
| 10 | | | | | | | |
| 11 | | | | | | | |
| 12 | | | | | | | |
| **Mean** (n=12) | 54.8 | 92.1 | 98.4 | 99.7 | 100.7 | 101.7 | 103.3 |
| **SD** | 9.4 | 4.5 | 3.3 | 2.8 | 2.4 | 2.1 | 1.8 |
| **% RSD** | 17.2 | 4.9 | 3.4 | 2.8 | 2.4 | 2.1 | 1.7 |

Reference: Notebook 2250, pp.136, 137 (Vessels 1-6); Notebook 2250, pp. 144, 145 (Vessels 7-12).
Lot 13105.003A-Batch release sample was tested using tested using TM-07-0233.

**Table 6. Complete Dissolution Profiles of PL2200 TBM Drug Product (No. 13105.006)**

**PL2200 Lot Number:** **13105.006**
**Speed:** 150 rpm
**Component Name:** Total Salicylates

| | Time (min) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Vessel** | **5** | **10** | **15** | **20** | **25** | **30** | **40** | **50** | **60** | **75** | **90** | **120** | **180** |
| 1 | (b) (4) | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | | |
| 5 | | | | | | | | | | | | | |
| 6 | | | | | | | | | | | | | |
| 7 | | | | | | | | | | | | | |
| 8 | | | | | | | | | | | | | |
| 9 | | | | | | | | | | | | | |
| 10 | | | | | | | | | | | | | |
| 11 | | | | | | | | | | | | | |
| 12 | | | | | | | | | | | | | |
| **Mean (n=12)** | 0.76 | 21.73 | 50.78 | 72.32 | 85.97 | 93.55 | 99.88 | 101.40 | 101.86 | 102.67 | 103.08 | 103.6 | 104.12 |
| **SD** | 0.34 | 4.63 | 7.07 | 5.71 | 3.07 | 2.17 | 2.54 | 2.71 | 2.73 | 2.77 | 2.74 | 2.86 | 3.01 |

Reference: Notebook 3031, pp. 168, 169.
See PII Study Report VR 3192 for complete details.

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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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TIEN MIEN CHEN
12/10/2012

ANGELICA DORANTES
12/10/2012

# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 203697 | Submission Date: 03/12/2012 |
| Relevant IND(s): | IND 074290 |
| Submission Type; Code: | 505 (b) (2) |
| Reference Drug: | Genuine Bayer® Aspirin tablets, 325-mg |
| Brand Name: | To-be-determined |
| Generic Name: | Aspirin |
| Formulation; Strength(s): | Immediate-release capsule, 325-mg |
| Clinical Pharmacology Reviewer: | Suresh B Naraharisetti, Ph.D. |
| Team Leader: | Yun, Xu, Ph.D. |
| OCP Division: | Division of Clinical Pharmacology II |
| OND Division: | Division of Nonprescription Clinical Evaluation |
| Sponsor: | PLx Pharma Inc. |
| Proposed Indication: | For temporary relief of minor aches and pains due headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pain of arthritis; and reduction of fever. |
| Proposed Dosage Regimen: | • Adults and children 12 years and over: take 1 or 2 capsules every 4 hours or 3 capsules every 6 hours, not to exceed 12 capsules in 24 hours.<br>• children under 12 years: consult a doctor |

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## 1.0 Executive Summary

### 1.1. Recommendation

The NDA 203697 is acceptable from a Clinical Pharmacology perspective provided that a satisfactory agreement is reached between Agency and Sponsor regarding the labeling language.

### 1.2 Phase 4 Commitments

None

### 1.3. Regulatory History

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 chiefly constitutes of a lipid component phosphotidylcholine, hereafter "PC". (b) (4)

Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. Aspirin is accepted 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 are identical to the indications outlined in the TFM for OTC internal analgesic products for oral administration:- 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.

The Sponsor could not pursue the straight forward monograph route for aspirin, rather required to submit a 505(b) (2) application due to the fact that Aspirin-PC formulation contains (b) (4) of lecithin. For an appropriate reference drug for 505(b) (2) application, the Sponsor was told during pre-IND meeting in 2007 that they could use any marketed 325-mg aspirin product that meets the requirements outlined in the TFM. Therefore, Sponsor used Genuine Bayer® Aspirin tablets, 325-mg as a reference drug in the pivotal bioequivalence study. No specific clinical safety and efficacy studies have been evaluated for this product and refer to the FDA's prior findings of safety and efficacy of aspirin set forth in the monograph (note: the monograph is tentative and is not final yet) as well as supportive literature references. During the pre-IND meeting stage in 2007, the Sponsor was told to prove that PC in the product is not an active ingredient and advised that they could use pharmacokinetic (PK) approach to demonstrate that PC does not interfere with the bioavailability of aspirin for the OTC pain reliever and fever reducer indications. Agency also added that clinical safety and efficacy studies would be required if bioequivalence is not demonstrated.


Aspirin is chemically 'acetylsalicylic acid'. As acetylsalicylic acid is rapidly hydrolyzed to the primary metabolite salicylic acid after oral administration, it was agreed during the pre-IND stage to use salicylic acid as the analyte for demonstrating bioequivalence for the proposed indication. Salicylic acid as a primary analyte for BE analysis for this product and was also used previously in the NDA review of Extra Strength Bayer Migraine drug product (NDA 21317; DARRTS dated 06/05/2001). From the mechanism of action point of view, 'salicylic acid' is the active moiety responsible for most anti-inflammatory and analgesic effects whereas 'acetylsalicylic acid' is the active moiety for the antiplatelet-aggregating effect.

### 1.4. Summary of Clinical Pharmacology Findings

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). The studies PL-ASA-001 and PL-ASA-003 is reviewed by this reviewer and the Study PL-ASA-002 was reviewed by the Medical Officer in DNCE. As pointed earlier, no specific clinical safety and efficacy studies have been evaluated for this product and the application refers to the FDA's prior findings of safety and efficacy of aspirin set forth in the TFM and literature references. Specifically, efficacy is supported from the general aspirin literature and safety from the general aspirin literature and review of aspirin adverse events in AERS.

Aspirin-PC formulations includes two to-be-marketed formulation batches, Lot 13105.003 and Lot 13105.006 and one test formulation batch Lot # 13105.001. The bioequivalence study was conducted with the 'test formulation' Lot # 13105.001B. Food effect was conducted with one of the to-be-marketed formulation Lot 13105.003 (Lot 13105.003A). 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 (email discussion) 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. For additional details, see Dr. Tien Mien Chen's review in DARRTS.

**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 study also evaluated the antiplatelet

pharmacodynamics of Aspirin-PC versus the reference drug. The Medical Officer in DNCE submitted a consult to OND1/DCRP on the antiplatelet- pharmacodynamics. This part was reviewed by Dr. Divya Menon-Anderson, clinical pharmacology reviewer of Division of Clinical pharmacology 1, (b) (4) For additional details see Dr. Divya Menon-Anderson's review in DARRTS dated 11/14/2012.

The details of the BE study conduct are listed in the bulleted points below.

- For 325-mg dose level, out of 16 subjects, 14 subjects completed both treatment arms. Two subjects, #116 (received only reference arm) and #117 (received only test arm) who received only one of the treatment arms, were excluded from the BE analysis.
- For 650-mg dose level, out of 16 subjects 15 subjects completed both treatment arms. One subject, #115 was incorrectly dosed 325-mg for Aspirin-PC treatment arm instead of 650-mg. This information of incorrect dosing along with supporting documents [case report forms (CRFs)] was submitted by Sponsor as a response to clinical pharmacology information request (sent with 74-day letter). Accordingly #115 was excluded form the BE analysis at 650 dose level.
- Subjects #103 in 325-mg dose and #123 in 650-mg dose in Aspirin-PC treatment arm have pre-dose salicylic acid concentrations, however these two subjects were included in the BE analysis as their pre-dose concentrations are less than 5% of the Cmax values.
- In Oct 9th response to clinical pharmacology information request, Sponsor proposed to exclude two subjects, #126 (325-mg) and #123 (650-mg) stating them as statistical outliers; however did not provided any further evidence. The plasma concentration time profiles for the Aspirin-PC (test) treatment arm of these two subjects mismatch between two doses, i.e., Subject 126 dosed 325 mg –profile appears as 650 mg dose and Subject 123 dosed 650 mg – profile appears as 325 mg dose. However per CRFs, the two subjects were correctly dosed for both test and reference treatment arms. These two subjects cannot be excluded without additional evidence and were included in the BE analysis.
- The Office of Scientific Investigations (OSI) audited the study PL-ASA-001 (Dr. Jyothi Patel's review, DARRTs dated 10/31/2012), and has recommended the exclusion of subjects 105, 126 and 116 in 325 mg group and 102 in 650 mg group, due to lack of revalidation results for processed batch stability and auto-sampler stability for the reinjected runs of these subjects. Based on OSI's recommendation, these subjects were excluded from the analysis.

The BE analysis for salicylic acid (the active moiety for pain) between Aspirin-PC and Bayer Aspirin® is shown in the Table 1.4. 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 Cmax $AUC_{0-t}$, $AUC_{0-inf}$ 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. Further details can be found in the QBR.

It is concluded that the Aspirin-PC capsule is bioequivalent to Bayer Aspirin® Tablets at 325-mg, but not at 650-mg dose level under fasting conditions. Aspirin being a broad therapeutic index drug with a total daily dose of up to 3900 mg and a long history for use, its safety or efficacy is generally well recognized. Even though Asprin-PC at 650-mg dose level failed to meet BE slightly on the lower CIs, this is not considered clinically significant based on discussion with the clinical team.

**Table 1.4:** 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 | **75.8** - 106.4 |
| 650 (n=14) | AUCinf | 91.3 | **78.0** - 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.

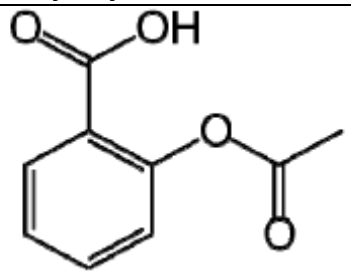
Administration of Aspirin-PC capsules with food resulted in a 6% lower AUC (AUC0-t and AUCinf) and a 22% lower Cmax for salicylic acid, respectively, and an approximately 1.64-hour delay in salicylic acid mean Tmax (4.58 hours vs 2.94 hours) compared to fasted conditions. The observed food effect for the Aspirin-PC product is not considered clinically significant and requires no dose adjustments. The 21 CFR 343.80 Subpart C– Labeling notes that the rate of absorption for aspirin from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents) and other physiologic factors. Enteric coated aspirin products are erratically absorbed from the GI tract. 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*. Therefore, the proposed product can be taken regardless of food.

*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.

## 2.0 Question Based Review

### 2.1 General Attributes of the Drug

**2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?**

| Table 2.1.1: Physical-Chemical Properties of Aspirin | |
|---|---|
| Drug Name | Aspirin (Acetyl Salicylic Acid) |
| Chemical Name | 2-acetyloxybenzoic acid |
| Structure |  |
| Molecular Formula | $C_9H_8O_4$ |
| Molecular Weight | 180.157 |

**2.1.2 What is the composition of the to-be-marketed formulation of Aspirin-PC?**

Asprin-PC capsules are an immediate-release lipid suspension of aspirin filled in a two-piece (b) (4) capsule. It contains 325-mg of aspirin, anhydrous citric acid, colloidal silicon dioxide, medium chain triglycerides, soy lecithin, FD&C Blue #1, and pharmaceutical ink. (b) (4) hypromellose, carrageenan, potassium chloride, and titanium dioxide. The quantitative composition is shown in the Table 2.1.2.

**Table 2.1.2.** Aspirin-PC Quantitative Composition and Function of Components

| Ingredient | Function | mg/capsule | Quality Standard |
|---|---|---|---|
| (b) (4) | | | |
| Aspirin (b) (4) | Active Ingredient | 325.0 | USP |
| Lecithin (b) (4) | (b) (4) | | DMF (3) |
| Medium Chain Triglycerides | | | NF |
| Anhydrous Citric Acid | | | USP |
| Colloidal Silicon Dioxide | | | NF |
| (b) (4) | | | |
| (b) (4) | | | |
| (b) (4) | (b) (4) | | DMF (3) |
| (b) (4) | | | |
| (b) (4) | (b) (4) | | USP |
| FD&C Blue #1 | | | FDA/EC |
| (b) (4) | | | USP |
| | | | USP |
| Total Weight | | 881.6 | |

Aspirin-PC formulations includes two to-be-marketed formulation batches, Lot 13105.003 and Lot 13105.006 and one test formulation batch Lot # 13105.001. The bioequivalence study (PL-ASA-001) was conducted with the 'test formulation' Lot #

13105.001B. Food effect was conducted with one of the to-be-marketed formulation Lot 13105.003 (Lot 13105.003A). Sponsor has submitted in vitro dissolution data to bridge the test formulation (Lot 13105.001) and two to-be-marketed formulation batches (Lot 13105.003 and Lot 13105.006). The ONDQA/Biopharmaceutics reviewer, Dr. Tien Mien Chen (email discussion) 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. For additional details, see Dr. Tien Mien Chen's review in DARRTS.

**2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?**
Aspirin is an NSAID. The exact mechanism of action of NSAIDs is unknown. NSAIDs are known to inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid through the inhibition of the enzyme cyclo-oxygenase (COX). The expression of the two isoenzymes of COX, COX-1 and COX-2, is differentially regulated. COX-1 is expressed constitutively at various levels, depending on tissue context: maintenance of gastric mucosal integrity, renal homeostasis and platelet aggregation. In contrast, COX-2 levels are undetectable and it is selectively up-regulated in response to inflammatory cytokines or trauma.

The proposed indications for Asprin-PC are identical to the indications outlined in the TFM for OTC internal analgesic products for oral administration: 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.

**2.1.4 What are the proposed dosage and route of administration?**
Aspirin-PC capsules are intended for oral administration. The proposed dosage for adults and children 12 years and over is to take 1 or 2 capsules every 4 hours or 3 tablets every 6 hours, not to exceed 12 capsules in 24 hours. The children under 12 years need to consult a doctor.

**2.1.5 What are the core studies submitted in this NDA?**
The clinical program for Aspirin-PC consisted of two core clinical pharmacology studies and a clinical GI safety study.
**Clinical pharmacology studies:**

- Pivotal Bioequivalence Study (PL-ASA-001): A randomized cross-over bioequivalence study of Asprin-PC versus Bayer Aspirin in healthy volunteers
- Food-Effect Study (PL-ASA-003): A randomized, cross-over food-effect study of Asprin-PC in healthy volunteers

**Clinical Safety study:**

- GI Safety Study: (PL-ASA-002): A randomized, 7-day, multiple-dose, single-blind, endoscopic evaluation of upper GI mucosal damage induced by Aspirin-PC versus Aspirin in healthy volunteers

Studies PL-ASA-001and PL-ASA-003 is reviewed by this reviewer and the Study PL-ASA-002 was reviewed by the Medical Officer in DNCE.

## 2.2 General Clinical Pharmacology

### 2.2.1. What are the general PK characteristics of the drug?

Orally administered aspirin is absorbed rapidly, partly from the stomach, but mostly from the upper intestine. The rate of absorption is determined by many factors: the disintegration and dissolution rate of the dosage form, the pH at the mucosal surfaces, and gastric emptying time. Salicylates are absorbed by passive diffusion, primarily of nondissociated salicylic acid, across gastrointestinal membranes, and the rate of absorption is influenced by gastric pH. Increasing gastric pH increases salicylate dissociation; however, increased gastric pH increases the solubility of salicylates, thus enhancing dissolution of the dosage form. The overall effect is enhanced absorption. The presence of food delays absorption of salicylates.

Ingested aspirin is mainly absorbed as acetylsalicylic acid, but enters the systemic circulation mainly as salicylic acid because of hydrolysis by esterases in the gastrointestinal mucosa and the liver. Hydrolysis in the plasma, liver and erythrocytes results in rapid disappearance of detectable acetylsalicylic acid. Both aspirin and salicylate have pharmacological activity; only aspirin has an anti-platelet effect.

After absorption, salicylate is distributed throughout most body tissues and most transcellular fluids, primarily by pH-dependent passive processes. The volume of distribution of usual doses of aspirin in normal subjects is about 170 ml/kg, increasing to about 500 ml/kg at high therapeutic doses because of saturation of binding sites on plasma protein. At normal clinical doses, 80% to 90% of the salicylate is bound to plasma proteins, especially albumin; this fraction declines as plasma concentrations are increased.

Salicylate is mainly eliminated by hepatic metabolism (primarily by hepatic conjugation). The metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption. The plasma half-life of acetylsalicylic acid is approximately 30 minutes, whereas salicylic acid is 2 to 3 hours in low doses.

### 2.2.2 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Aspirin is chemically ‘acetylsalicylic acid’. Since acetylsalicylic acid is rapidly converted to salicylic acid by hydrolysis and first-pass metabolism, peak plasma concentrations of acetylsalicylic acid are extremely sensitive to minor variations in solid dosage form dissolution and disintegration. In contrast, peak plasma concentrations of salicylic acid are relatively stable compared to acetylsalicylic acid and are considered to be a superior indicating variable for comparative PK bioequivalence. Hence, the Aspirin-PC PK studies are based on plasma salicylic acid concentration only. Salicylic acid as the analyte for bioequivalence (agreed pre-IND meeting in 2007), which is the active moiety responsible for most anti-inflammatory and analgesic effects.

## 2.3. Intrinsic Factors

### 2.3.1. What is the pediatric plan?

The Sponsor is requesting OTC monograph fever and pain indications and would like to label the product for those aged 12 and above. The Sponsor is requesting a full waiver for all pediatric age groups for the above indications because Aspirin-PC does not provide a meaningful benefit over existing therapies in pediatric patients and is not likely to be used in a substantial number of them.

Currently it being discussed with office of compliance whether this NDA product triggers PREA. In general, the excipients do not trigger PREA. The tentative PERC meeting is scheduled on 12//19/2012. While it is still under discussion, the pediatric studies 'may be" waived for fever indication due to aspirin's association with the risk of Reye syndrome. For pain indication pediatric studies 'may be" waived because aspirin of does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients.

The monograph is not final for fever and pain indications. The Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the Counter Human Use Tentative Final Monograph (TFM) lists dosing for children down to the age of 2 yrs. There is however professional labeling which has been finalized for vascular indications and rheumatologic disease indications. Dosing for juvenile rheumatoid arthritis starts at 90-130 mg/kg/day in divided doses, with increases as needed for an anti-inflammatory effect with target plasma salicylate levels of 150-300 µg/mL (21 CFR 343.80 Professional Labeling.)

## 2.4. General Biopharmaceutics

### 2.4.1. Is the Aspirin-PC Capsules bioequivalent to the reference, Genuine Bayer® Aspirin Tablets following single dose administration in fasting conditions?

Study PL-ASA-001 was randomized, 2-period, 2-sequence cross-over study. It is a pivotal bioequivalence study of the Aspirin-PC Capsules versus Genuine Bayer® Aspirin Tablets (reference product) at two dose levels, 325-mg and 650-mg (administered as two 325-mg capsules/tablets).

**Treatments:**

- 325-mg (1 x 325-mg; Aspirin-PC vs Genuine Bayer® Aspirin) (n=14)
- 650-mg (2 x 325-mg; Aspirin-PC vs Genuine Bayer® Aspirin) (n=15)
- Washout: 2 weeks between treatments
- Batch # 13105.001B - Aspirin- PC
- Batch # 253217 K – Bayer Aspirin

Serial plasma samples were collected pre-dose and 24 hours post-dose to determine salicylic acid, acetylsalicylic acid via validated LC-MS/MS assays. As acetylsalicylic

acid is rapidly hydrolyzed to the primary metabolite salicylic acid after oral administration, it was agreed during the pre-IND stage that salicylic acid is the analyte for bioequivalence analysis. From the mechanism of action point of view, 'salicylic acid' is the active moiety responsible for most anti-inflammatory and analgesic effects.

The study also evaluated the anti-platelet pharmacodynamics comparing Aspirin-PC versus the reference drug. This part was reviewed by Dr. Anderson, clinical pharmacology reviewer of Division of Clinical pharmacology 1, supporting the cardiovascular drugs therapeutic area.

**Results:**

**Plasma Salicylic acid Concentrations and PK parameters:**
The mean + SD plasma concentrations of salicylic acid (linear scale) over 24 hours are presented in Figure 2.4.1a for 325-mg and 650-mg dose levels. The median lag time (Tlag) for salicylic acid concentrations was longer for Aspirin-PC compared to Bayer Aspirin at both dose levels (Aspirin-PC vs. Bayer Aspirin: 15 min vs. 4 min for 325 mg; 15 min vs. 3 min, for 650 mg). For pain medications, the appearance of systemic concentrations at an earlier time is an important attribute for 'onset of pain-relief'.

The obtained PK parameters for salicylic acid were presented in Table 2.4.1a.

**Figure 2.4.1a:** Mean+SD salicylic acid concentration-time profiles (24 hours) after administration of Aspirin-PC Capsules and Bayer Aspirin® Tablets at 325-mg (1x 325-mg) and 650-mg (2 x 325-mg) dose levels. The OSI recommended subjects were excluded.

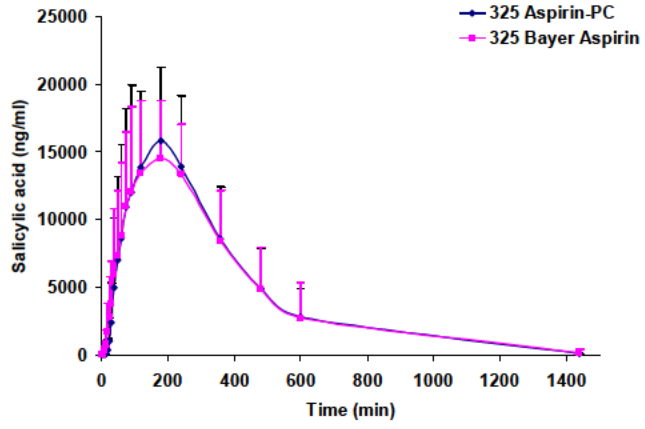
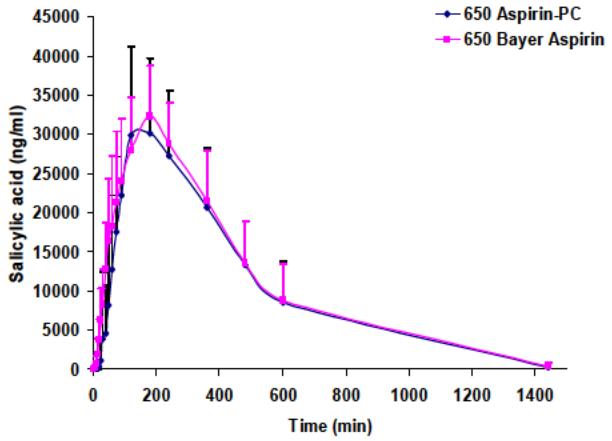
| 325-mg Aspirin-PC vs Bayer Aspirin® (n=12) | 650-mg Aspirin-PC vs Bayer Aspirin® (n=14) |
|---|---|
|  |  |

**Table 2.4.1a.** PK parameters of salicylic acid after administration of Aspirin-PC Capsules and Bayer Aspirin® Tablets at 325-mg (1x 325-mg) and 650-mg (2 x 325-mg) dose levels. The OSI recommended subjects were excluded.

| **Parameter** | **325-mg (1x 325-mg)** | | | | **650-mg (2 x 325-mg)** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Aspirin-PC** (n=12) [#] | | **Bayer Aspirin®** (n=12) [#] | | **Aspirin-PC** (n=14) [*] | | **Bayer Aspirin®** (n=14) [*] | |
| | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV |
| Cmax (µg/mL) | 18.0 | 30 | 16.8 | 25 | 35.1 | 25 | 34.1 | 17 |
| AUC0-t (min*µg/mL) | 5823 | 39 | 5995 | 47 | 14465 | 35 | 15791 | 30 |
| AUCinf (min*µg/mL) | 6228 | 45 | 6200 | 45 | 14722 | 33 | 15934 | 30 |
| T1/2 (min) | 148 | 28 | 161 | 44 | 149 | 22 | 165 | 26 |
| Tlag (min) | 15 | | 4 | | 14 | | 3 | |
| Tmax (min) Median (max, min) | 120 (75, 240) | | 150 (75, 240) | | 150 (120, 360) | | 180 (75, 240) | |

[#] Subjects, 116 and 117 received only one treatment, were excluded.
[*] Subject 115, incorrectly dosed was excluded.
OSI recommended subjects 105, 126 in 325 mg and 102 in 650 mg groups were excluded

**Salicylic acid Bioequivalence Analysis:**

The bioequivalence analysis was conducted for primary analyte salicylic acid at 325 and 650-mg dose levels. Following are the details of the subjects excluded from the bioequivalence analysis and the subjects with pre-dose concentrations.

- For 325-mg dose level, out of 16 subjects, 14 subjects completed both treatment arms. Two subjects, #116 (received only reference arm) and #117 (received only test arm) who received only one of the treatment arms, were excluded from the BE analysis.
- For 650-mg dose level, out of 16 subjects 15 subjects completed both treatment arms. One subject, #115 was incorrectly dosed 325-mg for Aspirin-PC treatment arm instead of 650-mg. This information of incorrect dosing along with supporting documents [case report forms (CRFs)] was submitted by Sponsor as a response to clinical pharmacology information request (sent with 74-day letter). Accordingly #115 was excluded form the BE analysis at 650 dose level.
- Subjects #103 in 325-mg dose and #123 in 650-mg dose in Aspirin-PC treatment arm have pre-dose salicylic acid concentrations, however these two subjects were included in the BE analysis as their pre-dose concentrations are less than 5% of the Cmax values.
- In Oct 9$^{th}$ response to clinical pharmacology information request, Sponsor proposed to exclude two subjects, #126 (325-mg) and #123 (650-mg) stating them as statistical outliers; however did not provided any further evidence. The plasma concentration time profiles for the Aspirin-PC (test) treatment arm of these two subjects mismatch between two doses, i.e., Subject 126 dosed 325 mg –profile appears as 650 mg dose and Subject 123 dosed 650 mg – profile appears as 325 mg dose. However per CRFs, the two subjects were correctly dosed for both test and reference treatment arms. These two subjects cannot be excluded without additional evidence and were included in the BE analysis. The PK profiles for these two subjects along with all other subjects comparing test and reference plasma concentrations, for doses 325 and 650 is shown in Figure 2.41b and Figure 2.41c, respectively.
- The Office of Scientific Investigations (OSI) audited the study PL-ASA-001 (Dr. Jyothi Patel's review, DARRTs dated 10/31/2012), and has recommended the exclusion of subjects 105, 126 and 116 in 325 mg group and 102 in 650 mg group, due to lack of revalidation results for processed batch stability and auto-sampler stability for the reinjected runs of these subjects. Based on OSI's recommendation, these subjects were excluded from the analysis.

**Figure 2.41b.** Individual salicylic acid concentration-time profiles by treatment (Dose=325; ASA-PC- Aspirin-PC, ASA- Bayer Aspirin). The OSI recommended subjects were excluded.

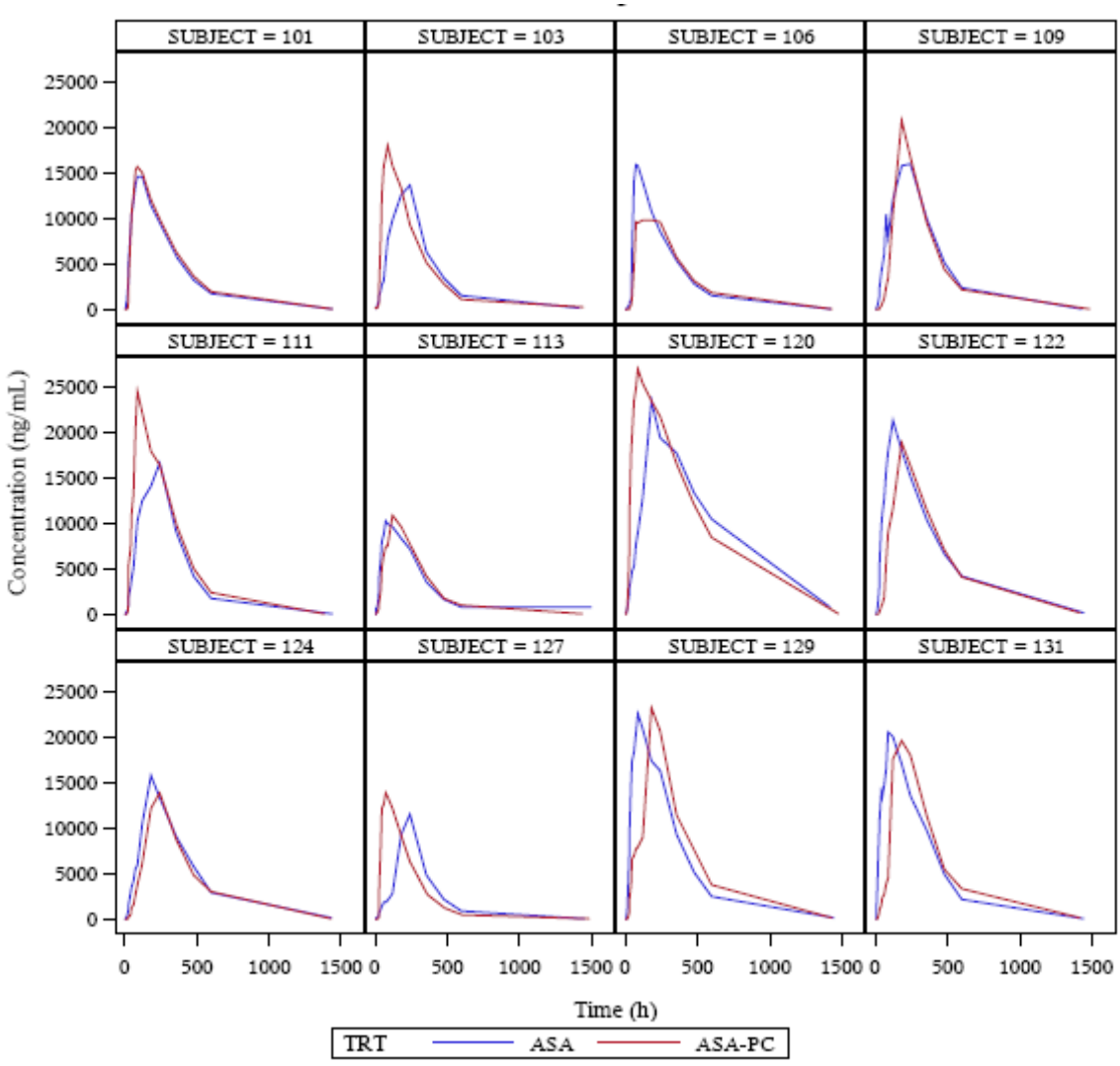
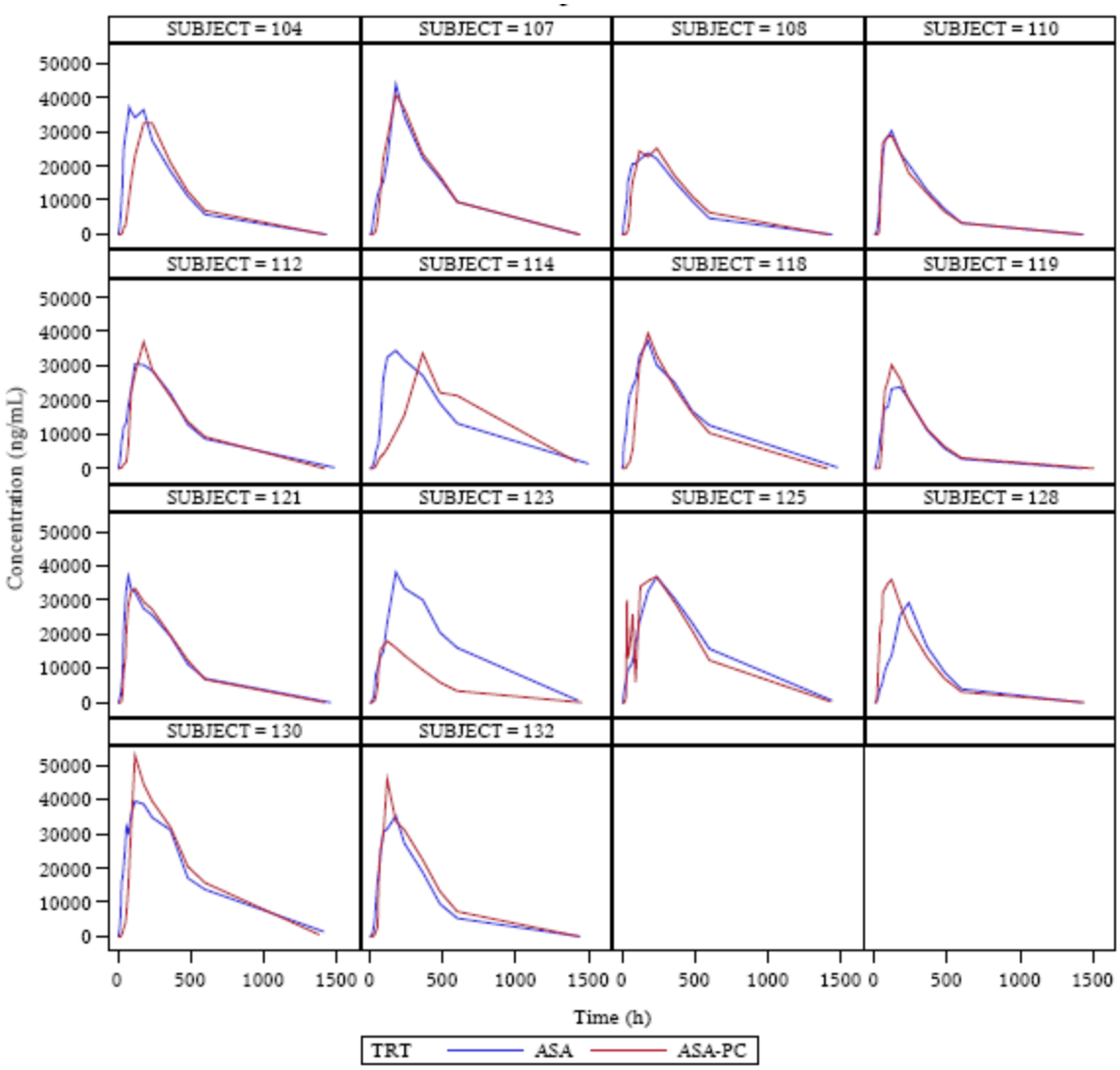


**Figure 2.41c.** Individual salicylic acid concentration-time profiles by treatment (Dose=650; ASA-PC- Aspirin- PC, ASA- Bayer Aspirin). The OSI recommended subjects were excluded.




The BE analysis for salicylic acid (the active moiety for pain) between Aspirin-PC and Bayer Aspirin® is shown in the Figure 2.4.1d and Table 2.4.1b. 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. At 325-mg dose level, the upper limit of 90% CI for log transformed salicylic acid Cmax $AUC_{0-t}$, $AUC_{0-inf}$ 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. It is concluded that the Aspirin-PC capsule is bioequivalent to Bayer Aspirin® Tablets at 325 mg, but not at 650 mg dose level under fasting conditions.

**Figure 2.4.1d:** Geometric means ratios and 90% confidence intervals for Cmax $AUC_{last}$ and $AUC_{inf}$ of Aspirin-PC Capsules and Bayer Aspirin® Tablets for 325-mg [(1x 325-mg), n=12] and 650-mg [(2 x 325-mg), n=14] dose levels. Geometric means for the treatments were based on least squares means of log-transformed PK parameter values. Figure shows that Aspirin-PC capsule is not bioequivalent to Bayer Aspirin® Tablets at both dose levels. The BE analysis in this figure is with OSI recommended exclusion of subjects.

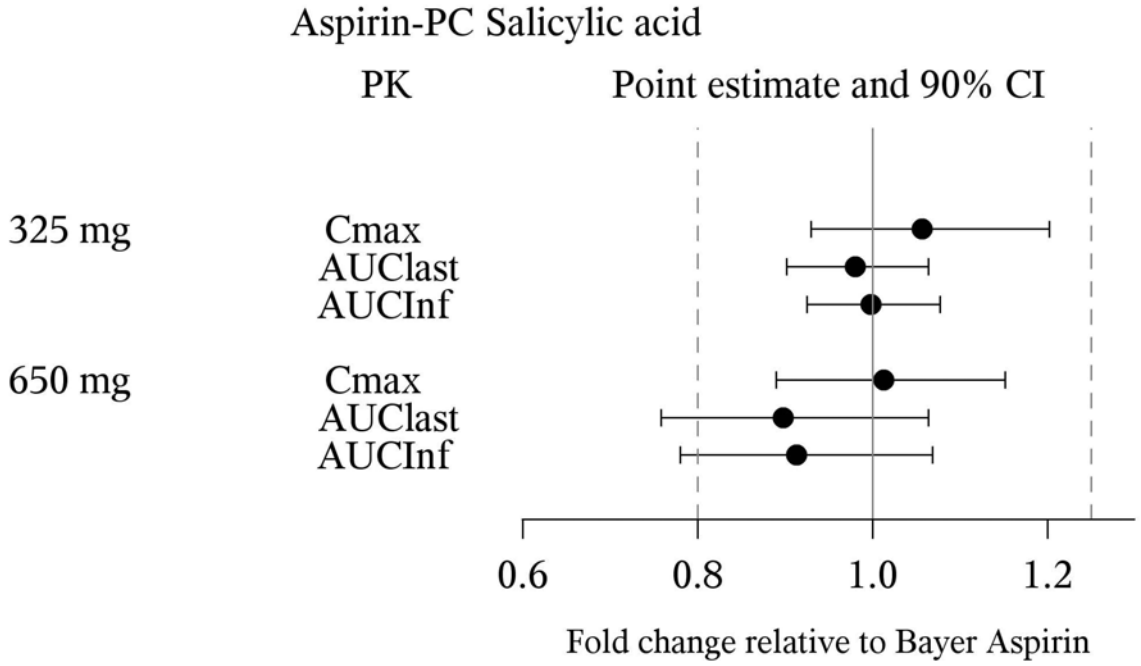



**Table 2.4.1b:** BE analysis for salicylic acid (the active moiety for pain) between Aspirin-PC and Bayer Aspirin®. The BE analysis was conducted with exclusion of subjects which OSI has recommended.

| 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 | **75.8** - 106.4 |
| 650 (n=14) | AUCinf | 91.3 | **78.0** - 106.9 |

It is concluded that the Aspirin-PC capsule is bioequivalent to Bayer Aspirin® Tablets at 325 mg, but not at 650 mg dose level under fasting conditions. Aspirin being a broad therapeutic index drug with a total daily dose up to 3900 mg and a long history for use, its safety or efficacy is generally well recognized. Even though Asprin-PC at 650 mg dose level failed BE slightly on the lower CI, this is not considered clinically significant based on discussion with the clinical team.

**Plasma Acetylsalicylic acid Concentrations and PK parameters:**

The mean + SD plasma concentrations of acetylsalicylic acid (linear scale) over 6 hours for 325-mg dose and 650-mg dose are presented in Figure 2.4.1e. Although acetylsalicylic acid concentrations were analyzed for all collected (24 hours) plasma samples, concentrations were detected only up to 6 hours in both Aspirin-PC and Genuine Bayer® Aspirin treatments. The median lag-time (Tlag) for acetylsalicylic acid concentrations was longer for Aspirin-PC compared to the reference Bayer Aspirin at both dose levels (Aspirin-PC vs. Bayer Aspirin: 16 min vs. 2 min for 325-mg; 15 min vs. 1 min for 650-mg). The PK parameters of acetylsalicylic acid were presented in Table 2.4.1c. The BE analysis for acetylsalicylic acid is shown in the Table 2.4.1d. The interpretation of acetylsalicylic acid PK and BE for anti-platelet aggregating effects was evaluated by Dr. Divya Menon-Anderson (Review, DARRTS dated 11/14/2012).

**Figure 2.4.1e:** Mean+SD acetylsalicylic acid concentration-time profiles (6 hours) after administration of Aspirin-PC Capsules and Bayer Aspirin® Tablets at 325-mg (1x 325-mg) and 650-mg (2 x 325-mg) dose levels. The OSI recommended subjects were excluded.

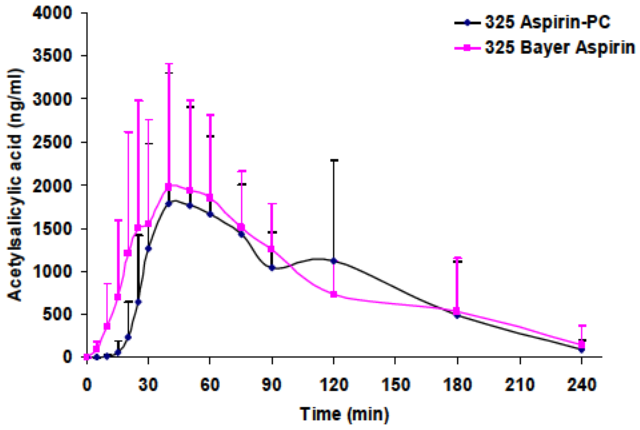
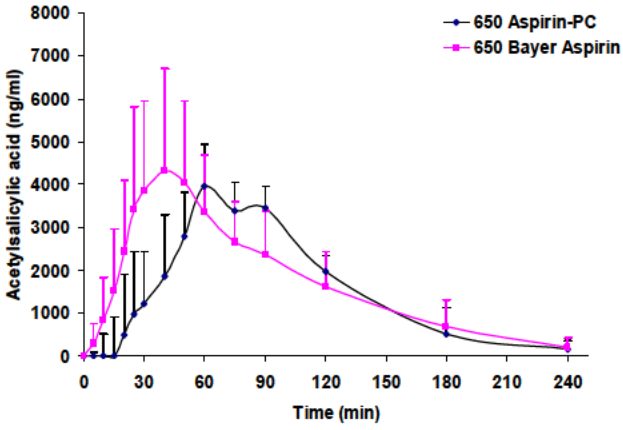
| 325-mg Aspirin-PC vs.Bayer Aspirin® (n=12) | 650-mg Aspirin-PC vs. Bayer Aspirin® (n=14) |
|---|---|
|  |  |

**Table 2.4.1c.** PK parameters of acetylsalicylic acid after administration of Aspirin-PC Capsules and Bayer Aspirin® Tablets at 325-mg (1x 325-mg) and 650-mg (2 x 325-mg) dose levels. The OSI recommended subjects were excluded.

| **Parameter** | **325-mg (1x 325-mg)** | | | | **650-mg (2 x 325-mg)** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Aspirin-PC** (n=12) | | **Bayer Aspirin®** (n=12) | | **Aspirin-PC** (n=14) | | **Bayer Aspirin®** (n=14) | |
| | Mean | %CV | Mean | %CV | Mean | %CV | Mean | %CV |
| Cmax (µg/mL) | 2.77 | 32 | 2.59 | 55 | 5.68 | 44 | 5.10 | 46 |
| AUC0-t (min*µg/mL) | 196 | 28 | 211 | 31 | 367 | 27 | 413 | 26 |
| AUCinf (min*µg/mL) # | 182 | 26 | 230 | 25 | 356 | 26 | 437 | 29 |
| T1/2 (min) # | 41 | 91 | 31 | 51 | 30 * | 52 | 55 | 129 |
| Tlag (min) | 16 | | 2 | | 15 | | 1 | |
| Tmax (min) Median (min, max) | 60 (40- 180) | | 68 (20 - 240) | | 60 (25 - 120) | | 40 (25- 90) | |

# n=8 , * n=12

**Table 2.4.1d:** BE analysis for acetylsalicylic acid. The OSI recommended subjects were excluded in the BE analysis.

| Dose | Dependent | Geometric Mean Ratio | 90% CI (Lower- Upper) |
|---|---|---|---|
| 325 | Cmax | 119.0 | 78.4 - 180.6 |
| 325 | AUC0-t | 95.1 | 82.5 - 109.7 |
| 325 | AUCinf | 85.7 | 68.5 - 107.2 |
| 650 | Cmax | 108.5 | 79.6 - 147.8 |
| 650 | AUC0-t | 86.5 | 76.5 - 97.8 |
| 650 | AUCinf | 90.1 | 81.0 - 100.3 |

**2.4.2 What is the effect of food on the BA of G-ER?**

The food effect for Aspirin-PC was evaluated using FDA recommended high fat food in the the study PL-ASA-003.

**Treatments:**

- Aspirin-PC (650-mg administered as two 325-mg capsules) under fasted conditions
- Aspirin-PC (650-mg administered as two 325-mg capsules) under fed conditions
- Washout: 7 days between treatments

The formulation used in the food effect study was from lot# 13105.003A

A total of 20 subjects were treated and all subjects completed both fasted and fed treatments. However, OSI has recommended exclusion of subjects 007 and 008 for food effect study. These two subjects were excluded in the food effect analysis.

**Results:**

**Plasma Salicylic acid Concentrations and PK parameters:**

The mean + SD plasma concentrations of salicylic acid (linear scale) over 24 hours comparing fasted versus fed conditions are presented in Figure 2.4.2a. For Aspirin- PC the median lag-time (Tlag) for salicylic acid concentrations under fed conditions was 36 minutes compared to 13 minutes under fasted conditions. The PK parameters of salicylic acid for fasted and fed conditions were presented in Table 2.4.2a.

Administration of Aspirin-PC capsules with food resulted in a 6%, lower AUC (AUC0-t and AUCinf) and 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. The 21 CFR 343.80 Subpart C–Labeling notes that the rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents) and other physiologic factors. Enteric coated aspirin products are erratically absorbed from the GI tract. 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*. Therefore, the proposed product can be taken regardless of food.

*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.

**Figure 2.4.2a:** Mean+SD salicylic acid (24 hours) concentration-time profiles after administration of Aspirin-PC Capsules 650-mg (2 x 325-mg) under fasted and fed conditions. The OSI recommended subjects were excluded.

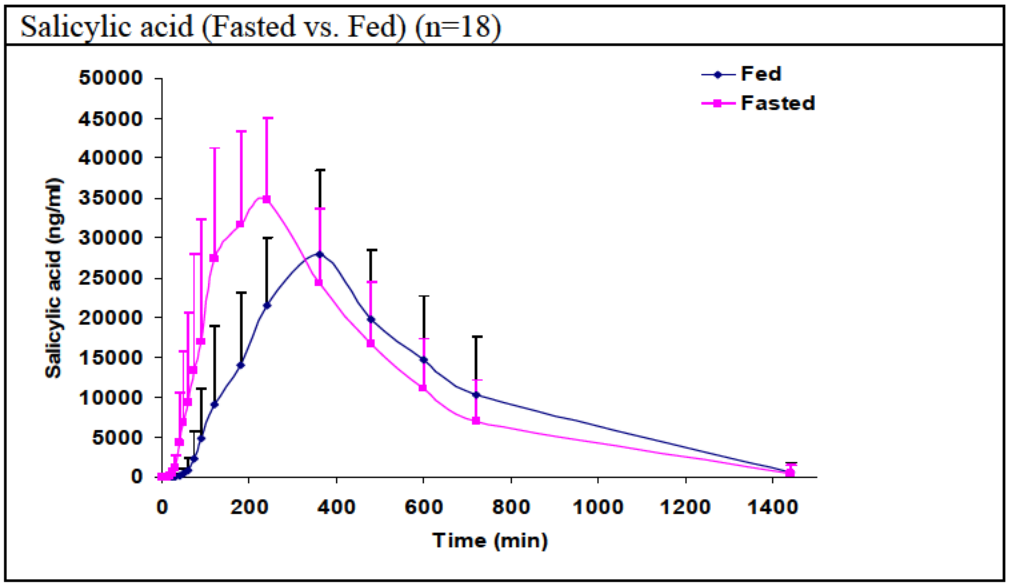


**Table 2.4.2a.** PK parameters of salicylic acid after administration of Aspirin-PC capsules (2 x 325-mg) under fasting and fed conditions. The OSI recommended subjects were excluded.

| **Parameter** | **Fed** (n=18) | | **Fasted** (n=18) | | **Mean Ratio (Fed /Fasted)** |
|---|---|---|---|---|---|
| | Mean | %CV | Mean | %CV | |
| Cmax (µg/mL) | 30.23 | 29 | 38.89 | 26 | 0.78 |
| AUC0-t (min*µg/mL) | 15111 | 44 | 16116 | 38 | 0.94 |
| AUCinf (min*µg/mL) | 15387 | 45 | 16402 | 39 | 0.94 |
| T1/2 (min) | 152 | 29 | 153 | 29 | |
| Tlag (min) | 36 | | 13 | | |
| Tmax (min) | 275 | 36 | 176 | 29 | |
| Tmax (min) Median (min, max) | 300 (90 – 360) | | 180 (90- 240) | | |

**Plasma Acetylsalicylic acid Concentrations and PK parameters:**
The mean + SD plasma concentrations of acetylsalicylic acid (linear scale) comparing fasted versus fed conditions are presented in Figure 2.4.2b. For Aspirin- PC the median lag-time (Tlag) for acetylsalicylic acid concentrations under fed conditions was much longer of 52 minutes compared to 15 minutes under fasted conditions. The PK parameters of acetylsalicylic acid for fasted and fed conditions were presented in Table 2.4.2b. Administration of Aspirin-PC capsules with food resulted in a 9% lower, 3% higher and 43% lower AUC0-t, AUCinf and Cmax of acetylsalicylic acid, respectively, and 63 min delay in mean Tmax (174 min vs 111 min) compared to fasted conditions. A 59% lower Cmax and 40 min delay in mean Tmax for acetylsalicylic acid using immediate release aspirin was observed in the food effect study by Koch et al. 1978*.

**Figure 2.4.2b:** Mean+SD acetylsalicylic acid (24 hours) concentration-time profiles after administration of Aspirin-PC Capsules 650-mg (2 x 325-mg) under fasted and fed conditions. The OSI recommended subjects were excluded.

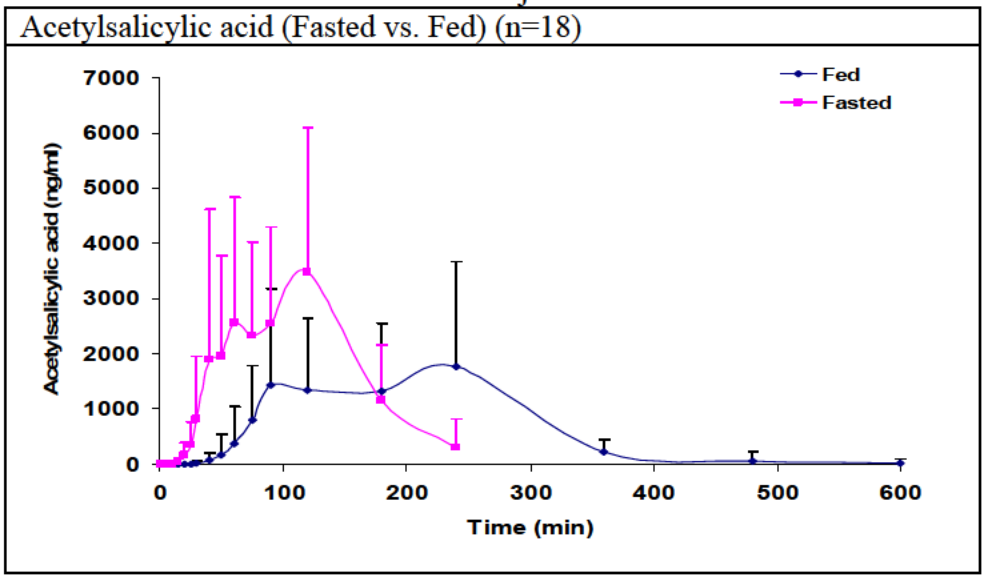


**Table 2.4.2b.** PK parameters of acetylsalicylic acid after administration of Aspirin-PC capsules (2 x 325-mg) under fasting and fed conditions. The OSI recommended subjects were excluded.

| **Parameter** | Fed (n=18) | | Fasted (n=18) | | **Mean Ratio (Fed /Fasted)** |
|---|---|---|---|---|---|
| | Mean | %CV | Mean | %CV | |
| Cmax (µg/mL) | 3.2 | 59 | 5.6 | 49 | 0.57 |
| AUC0-t (min*µg/mL) | 371 | 44 | 406 | 26 | 0.91 |
| AUCinf (min*µg/mL) | 416[#] | 23 | 405[Φ] | 27 | 1.03 |
| T1/2 (min) [#] | 70[#] | 66 | 24[Φ] | 26 | |
| Tlag (min) | 52 | | 15 | | |
| Tmax (min) | 174 | 41 | 111 | 37 | |
| Tmax (min) Median (min, max) | 210 (75 – 240) | | 120 (40 – 180) | | |

#N=9 ; ΦN= 5

## 2.5.Analytical Section

### 2.5.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

The OSI has audited the clinical and analytical sites for the conducted Clinical Pharmacology and Bio-analytical studies. See OSI inspection results in section 2.6

The plasma concentrations of salicylic acid and acetyl salicylic acid were analyzed using validated HPLC-MS/MS assays. The analytical assay has the following performance characteristics:

| | **Acetylsalicylic Acid** | **Salicylic Acid** |
|---|---|---|
| **Linear Range** | 50 – 24,000 ng/mL | 50 – 24,000 ng/mL |
| **Lower Limit of Quantitation** | 50 ng/mL | 50 ng/mL |
| Accuracy | 114.2% | 114.4% |
| **Intra-Run Precision (CV)** | | |
| 150 ng/mL | 2.4% | 5.0% |
| 3000 ng/mL | 2.6% | 2.2% |
| 20,000 ng/mL | 1.3% | 2.7% |
| **Intra-Run Accuracy** | | |
| 150 ng/mL | 108.7% | 92.7% |
| 3000 ng/mL | 99.4% | 96.6% |
| 20,000 ng/mL | 102.2% | 100.5% |
| **Inter-Run Precision (CV)** | | |
| 150 ng/mL | 8.4% | 7.5% |
| 3000 ng/mL | 5.1% | 5.1% |
| 20,000 ng/mL | 10.4% | 6.0% |

**Inter-Run Accuracy**

| | | |
|---|---|---|
| 150 ng/mL | 102.9% | 88.7% |
| 3000 ng/mL | 94.7% | 95.7% |
| 20,000 ng/mL | 95.6% | 97.8% |

### 2.6. OSI Inspection Results

The Office of Scientific Investigations (OSI) has issued Form FDA-483 at the analytical site (b) (4) during the inspection of studies PL-ASA-001 and PL-ASA-003. Additional details can be found in OSI review by Dr. Jyothi Patel in the DARRTs dated 10/31/2012. The OSI review states that the analytical data for subjects 102, 105, 126 and 116 (acetylsalicylic acid and salicylic acid) from Study PL-ASA-001, and subjects 007 and 008 (salicylic acid only) from Study PL-ASA-003 are not considered reliable until revalidation results submitted. These subjects were excluded from the analysis for BE and food effect studies.

## 3. Detailed Labeling Recommendations

Since this is an OTC product, there is no clinical pharmacology information included in the label. The labeling comments will be incorporated directly into the sponsor's proposed label after discussion with the review team.

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

### 4.3 Cover Sheet and OCPB Filing/Review Form

On **initial** review of the NDA/BLA application for filing:

| Office of Clinical Pharmacology<br>New Drug Application Filing and Review Form | | | |
|---|---|---|---|
| ***General Information About the Submission*** | | | |
| | **Information** | | **Information** |
| **NDA/BLA Number** | ***NDA*-203697** | **Brand Name** | |
| **OCP Division (I, II, III, IV, V)** | ***II*** | **Generic Name** | ***Aspirin, 325-mg*** |
| **Medical Division** | ***DNCE*** | **Drug Class** | ***Salicylates*** |
| **OCP Reviewer** | ***Suresh B Naraharisetti*** | **Indication(s)** | ***OTC –Pain indications*** |
| **OCP Team Leader** | ***Yun Xu*** | **Dosage Form** | ***Immediate- release Capsule*** |
| **Pharmacometrics Reviewer** | | **Dosing Regimen** | |
| **Date of Submission** | | **Route of Administration** | ***Oral*** |
| **Estimated Due Date of OCP Review** | | **Sponsor** | **PLx Pharma** |
| **Medical Division Due Date** | | **Priority Classification** | |
| **PDUFA Due Date** | **January 14, 2013** | | |

| ***Clin. Pharm. and Biopharm. Information*** | | | | |
|---|---|---|---|---|
| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | | | | |
| **Tabular Listing of All Human Studies** | | | | |
| **HPK Summary** | | | | |
| **Labeling** | | | | |
| **Reference Bioanalytical and Analytical Methods** | **X** | **1** | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |

| | | | | |
|---|---|---|---|---|
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD -** | | **2** | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | **X** | **1** | | **Pivotal BE study** |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | **X** | **1** | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | **Sponsor is requesting a waiver** |
| **Literature References** | | | | |
| **Total Number of Studies** | | **5** | | |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | X | | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | X | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | X | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | X | | | |
| 5 | Has a rationale for dose selection been submitted? | X | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | X | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | X | | | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | X | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | X | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | | | X | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**
**Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

***Comments to be communicated to the Sponsor in the Day-74 letter***

- ***After preliminary review for your data, it appears that after inclusion of all subjects in the BE analysis, your product failed to meet the BE criteria at both dose levels of 325 and 650-mg. Whether this is acceptable for approval of your NDA will be a review issue.***
- ***For 325-mg dose, you indicated that the upper limits of the 90% CI for both AUC and $C_{max}$ failed to meet the BE criteria because of the two influential outliers. Provide rationale for why these two subjects were considered as influential outliers, and reason leading to different PK exposure of these two subjects. Provide subject numbers of these two outliers as well as BE analysis results with and without these two subjects.***

- ***For 650-mg dose, you indicated subject 115 as an influential outlier and excluded this subject from BE analysis. In Section 16.1.13, Outlier Exclusion Summary, you showed that inclusion of this subject failed the BE criteria for lower limit of 90% CI for AUC. Provide plasma concentration-time data and PK parameters for this subject. Provide rationale why this subject should be excluded from the BE analysis, and reason leading to the different PK exposure of this subject. Provide BE analysis results with and without this subject.***
- ***Taking your product with food results in 22% lower Cmax in comparison to the fasted state. You indicated that this is consistent with results reported in the published literature on the effects of food on aspirin bioavailability of various dose forms, and with information provided in the 21 CFR 343 aspirin (internal analgesic) monograph. Whether the food effect result for your product is consistent with other Aspirin products will be a review issue.***

**BACKGROUND**

PLx Pharma submitted a 505 (b) (2) NDA for PL 2200 as an immediate-release oral capsule consisting of aspirin, a non-steroidal anti-inflammatory drug, formulated in a lipid suspension of soybean-derived lecithin. Each capsule contains 325-mg of aspirin USP (active ingredient) and (b) (4) of soy lecithin. The product is being developed as an analgesic/antipyretic for over-the-counter (OTC) use. (b) (4)

PLx Pharma (PLx) is seeking the clinical indications for aspirin outlined in the Tentative Final Monograph for OTC internal analgesic products for oral administration: as a fever reducer and analgesic indicated for the temporary relief of headaches, muscle pain, toothache, pain and fever of colds, and minor pain of arthritis.

As a 505(b) (2) NDA: Sponsor is relying on the Agency's findings on the safety and efficacy of aspirin. In support of this NDA, sponsor conducted the following Clinical Pharmacology/Clinical studies:

- Two PK studies in healthy volunteers
  - Pivotal Bioequivalence Study (PL-ASA-001):
    - A Randomized, Actively Controlled, Cross-Over Bioequivalence Study of PL2200 Versus Bayer Aspirin in Healthy Volunteers
  - Food-Effect Study (PL-ASA-003) :
    - A Randomized, Actively Controlled, Cross-Over Food-Effect Study of PL2200 in Healthy Volunteers

- One Safety study in healthy volunteers:
  - GI Safety Study: (PL-ASA-002):
    - A Randomized, Single-blind, Endoscopic Evaluation Of Upper GI Mucosal Damage Induced By Aspirin-PC (Pl2200) Versus Aspirin In Healthy Volunteers

The conducted PK studies meet the regulatory requirements for filing and this application is filable from the clinical pharmacology perspective. Additional details of the application and conducted clinical pharmacology studies can be found in the slides presented in the filing meeting dated 04/30/2012, attached to this tracking sheet. Based on the preliminary review, the above comments need to be communicated to the sponsor in 74-day letter.

| | |
|---|---|
| Suresh Babu Naraharisetti | May 3, 2012 |
| Reviewing Clinical Pharmacologist | Date |
| Xu Yun | May 3, 2012 |
| Team Leader/Supervisor | Date |

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/s/

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SURESH B NARAHARISETTI
12/07/2012

YUN XU
12/07/2012

# Office of Clinical Pharmacology
# Consult Review

| | |
|---|---|
| NDA | 203-697 |
| Drug / Sponsor | PL2200 / PLx Pharma |
| Consult date | 08/16/2012 |

**Background**

PL2200 is a modified formulation of aspirin containing 325 mg of aspirin dispersed in (b) (4) of lecithin (b) (4) in a hard (b) (4) capsule. (b) (4) In this submission the (b) (4) This document (b) (4) contains a review of the aspirin component of studies PL-ASA-001 (bioequivalence) and PL-ASA-003 (Food effect).

**Recommendation**

(b) (4)

The review specifically addressed the following questions.

1. Are the analytical methods used appropriate to quantify the following?
   a. Effect of aspirin on anti-platelet activity
      Yes, inhibition of serum thromboxane B2 (sTxB2) and agonist induced platelet aggregation, the two methods used in this study, are generally appropriate to quantify the anti-platelet activity of acetylsalicylic acid (ASA).

      The antiplatelet effect of ASA is a result of inhibition of TxA2 mediated platelet activation and aggregation. TxA2 is a short lived lipid that is metabolized to TxB2, which is more stable. Serum TxB2 can be measured with good accuracy and precision using radioimmunoassay or LC-MS techniques in serum or in platelet rich plasma following platelet activation[1,2].

   b. Differences in anti-platelet activity
      Inhibition of sTxB2 and agonist induced platelet aggregation, the two main methods used to assess anti-platelet effects of ASA in this study, are not sensitive to differences in ASA concentrations at doses above 100 mg.

      A dose dependent effect on sTxB2 is observed in the dose range of up to 100 mg, with > 90% inhibition of sTxB2 at 100 mg (**Figure 1**)[3], suggesting that close to maximal effect on sTxB2 inhibition is attained following administration of 100 mg ASA.

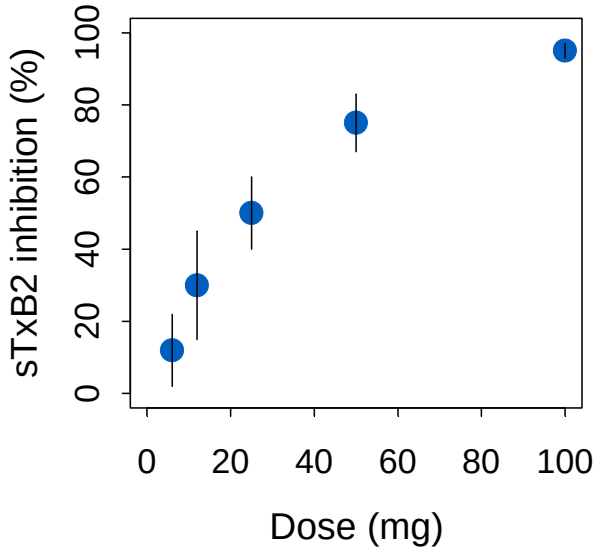


**Figure 1** Inhibition of platelet TxB2 production by oral aspirin. TxB2 production during whole blood clotting was measured before and 24 h after aspirin ingestion. The results are expressed as percent inhibition, each subject serving as his/her own control. Mean values ± SD are plotted. Adapted from reference # 3.

This is further supported by the observation (**Figure 2)** that 300 and 500 mg dose of ASA lie on the upper plateau of the dose-response curve for ASA [4],

[1] *Fitzpatrick et al, Anal Biochem, 1977 (82) 1-7*
[2] *Fitzpatrick et al, Prostaglandins, 1977 (13) 201-208*
[3] *Patrignani et al, J Clin Invest, 1982 (69) 1366-1372*
[4] *Burke et al, Am Heart J, 1995 (130) 465-472*

making it impossible to detect differences in the pharmacodynamic activity of ASA via inhibition of sTxB2 or platelet aggregation.

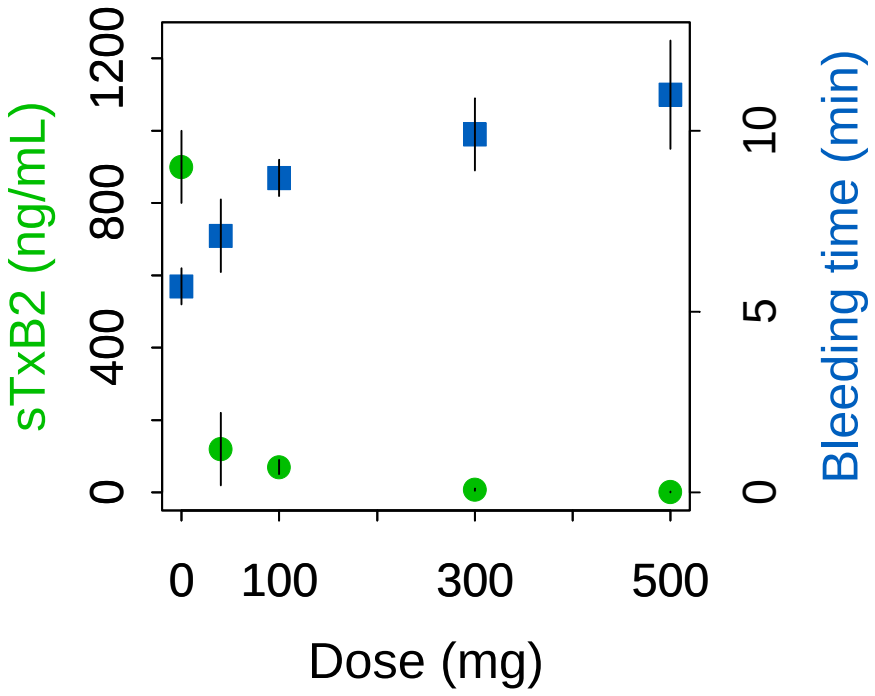


**Figure 2** Effect of aspirin (0, 40, 100, 300, and 500 mg) in healthy volunteers on (1) platelet thromboxane B2 (circles) generation 24 hours after oral administration of aspirin and (2) bleeding time (squares) 2 hours after oral administration of asprin. Mean values ± SE are plotted. Adapted from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

Therefore, these methods at the doses studied are not sensitive to detect differences in the anti-platelet activity of ASA between products at the studied doses (325 mg & 650 mg).

2. Is the product equivalent to aspirin in terms of its PD profile when used for its anti-platelet effect?

The pharmacodynamic assays used in this study, sTxB2 and platelet aggregation, are not sensitive to ASA doses above 100 mg. As expected maximal inhibition of sTxB2 as well as platelet aggregation was observed with both dosage forms at the 325 and 650 mg (administered as 2x 325) dose levels. Hence, equivalence of the products based on PD cannot be evaluated.

However, for small molecules when PK equivalence for the moiety of interest is demonstrated, pharmacodynamic equivalence is implied. Therefore, an evaluation of the relative bioavailability of ASA, the active moiety responsible for the antiplatelet effect can address the question. As seen in **Figure 3** (on Page 9 of the review), the geometric mean ratio (GMR) and the 90% confidence interval for $AUC_{0-4}$ for ASA is contained

within 80 – 125% suggesting that PK is similar between PL220 and Bayer Aspirin. Given that the upper bound of the GMR for $C_{max}$ is greater than 125%, the products cannot be judged bioequivalent.

**Other findings**

The bioavailability of acetylsalicylic acid following administration of PL2200 with standard high fat FDA recommended meal is decreased (~25% for $AUC_{0-4}$ and ~50% for $C_{max}$) compared to administration of PL2200 fasted.

## Study PL-ASA-001 (Pharmacokinetic and pharmacodynamic bioequivalence)

| **Study Protocol #** PL-ASA-001 | **Study period** 02/11/2008 to 06/10/2008 |
|---|---|

**Title**

A randomized actively (sic) controlled cross-over bioequivalence study of aspirin-PC (ASA-PC, PL2200) versus aspirin in healthy volunteers.

**Objectives**

To assess systemic exposure to aspirin and salicylic acid, and the anti-platelet effect of aspirin following administration of PL2200 (325 mg and 2x325 mg) relative to that following administration of Genuine Bayer® aspirin (325 mg and 2x325 mg).

> *Reviewer's comment: For a product seeking approval via the 505(b)(2) pathway, relative bioavailability to a reference listed rug (RLD) should be determined at all strengths intended for marketing and not doses at which the product may be used. Only a single strength of PL2200 (325 mg) was developed. BE comparisons at the 650 mg dose level were made using two capsules of PL200 and two tablets of Genuine Bayer aspirin. Therefore, in this review, only data from the 325 mg portion of the study will be discussed. If there are any significant findings relating to the 2x325 mg portion of the study, those will be noted as well.*

**Study Design**

Open label, randomized, two period, two treatment crossover study, with a minimum of 14 days of washout between study periods.

**Study medication**

| | | |
|---|---|---|
| Dosage Form | PL2200 capsule | Genuine Bayer aspirin tablet |
| Dosage Strength | 325 mg | 325 mg |
| Batch #. | 13105.001B | 253217k |
| Administration | oral | |

**Sampling schedule**

Pharmacokinetics: Blood samples were collected for pharmacokinetic analysis at pre-dose, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90 minutes and 2, 3, 4, 5, 6, 8, 10, and 24 hours post-dose.

Pharmacodynamics: Blood samples were collected for measuring (1) serum thromboxane B2 at pre-dose, 2, 4, 6, 8, 10, and 24 hours post-dose and (2) platelet aggregation at pre-dose, 6 and 24 hours post-dose.

Blood samples were also collected before randomization and prior to crossover to assess platelet response to arachidonic acid.

**Data Analysis Methods**

Summary statistics were calculated and presented for PK and sTxB2 (considered primary

endpoint for PD) measures. ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

*Reviewer's comment: Although not specified in the sponsor's analysis plan, the PK measure AUC 0-4h was used for determining BE. For a drug with short elimination half-life such as ASA, it is acceptable to use AUC 0-4h as the PK measure for determining BE instead of AUC 0-inf.*

**Study population**

| | 325 mg | 650 mg |
|---|---|---|
| Randomized/Completed/ Discontinued Due to AE | 16/14/0 | 16/16/0 |
| Age (SD) years | 36.7 (10) | 36.9 (10) |
| Male/Female | 6/10 | 6/10 |
| Race (Caucasian/Black/Asian/American Indian or Alaska native/other) | 8/7/1/0 | 10/6/0 |

**Results:**

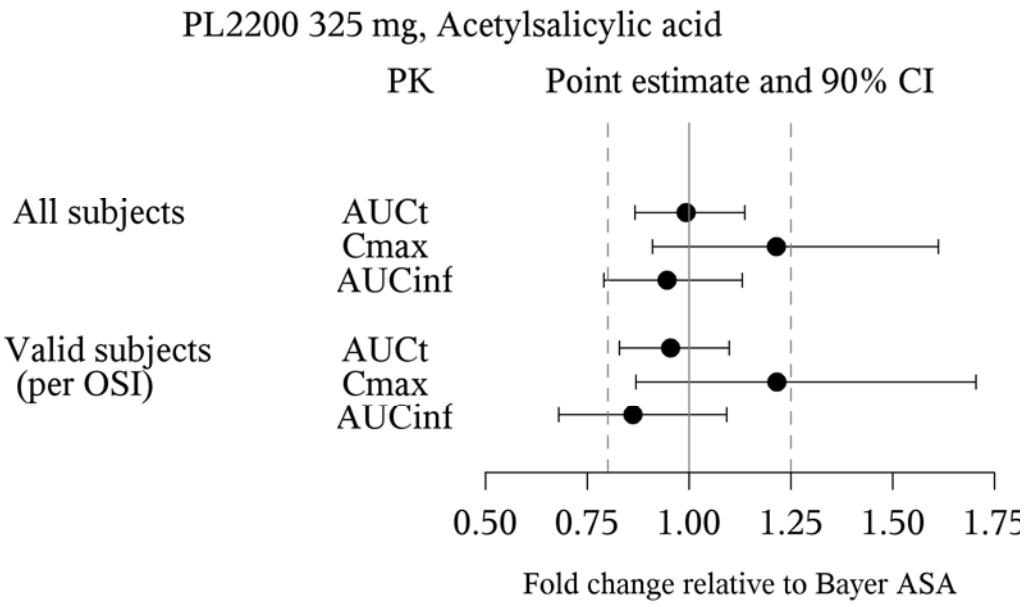


**Figure 3** PL2200 meets the BE criteria for AUC 0-4h. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean.

*Reviewer's comments:*

*(1) PL2200 is not bioequivalent to Genuine Bayer aspirin because the point estimate and 90% CI do not lie within the pre-specified limits for both $AUC_{0-t}$ and $C_{max}$. Because of its short half life of ~ 20 minutes, ASA levels in plasma are usually undetectable in about 3 hours post oral administration. Hence, comparison of AUC 0-4 h is more relevant.*

*However, $C_{max}$ was about ~25% higher for the test product. This observed increase can be considered negligible given that an increase in dose from 300 to 500 mg resulted in an average increase of about 1 minute in bleeding time (Figure 2). Further, from a GI tolerability perspective, this increase in $C_{max}$ may not be clinically relevant given the high doses of aspirin under consideration.*

*(2) The pharmacodynamic assays used in this study, sTxB2 and platelet aggregation, are not sensitive to ASA doses above 100 mg. As expected maximal inhibition of sTxB2 as well as platelet aggregation was observed with both dosage forms at the 325 and 2x 325 mg dose levels.*

*(3) Analysis excluding subjects 105, 116, and 126 (per OSI's tentative recommendation) are presented under the heading 'valid subjects'. Please refer to 'conc-time course' section for individual plasma ASA time courses.*

**Assay Method**

Acetylsalicylic acid and sTxB2 were measured using validated HPLC-MS/MS methods. The performance of the assay methods during study sample analysis is acceptable and is summarized in the table below.

| Analyte | ASA | sTxB2 ˄ |
|---|---|---|
| Method | LC/MS/MS | LC/MS/MS |
| LOQ (ng/mL) | 50 | 1 |
| Range (ng/mL) | 50 to 24000 | 1 to 500 |
| QCs (ng/mL) | 15, 3000, 20000 | 3, 100, 400 |
| Accuracy/Bias (%) | ± 9 | ± 5 |
| Precision (%CV) | ± 10.4 | ± 4 |

˄Blood samples were incubated at 37 C for 1 h for thromboxane generation

Agonist (arachidonic acid, 1.6 mM and collagen, 4 µg/ml) induced platelet aggregation was assessed using light transmission aggregometry following standard protocol.

> *Reviewer's comment: High dose collagen (4 to 5 µg/ml) is not sensitive to aspirin inhibition and results of such studies are uninterpretable.*

**Safety** Death/SAE: None

**Conclusion**

Total systemic exposure to ASA following a single dose of PL2200 is similar to that observed following a single dose of Bayer ASA.

**Concentration - time course**

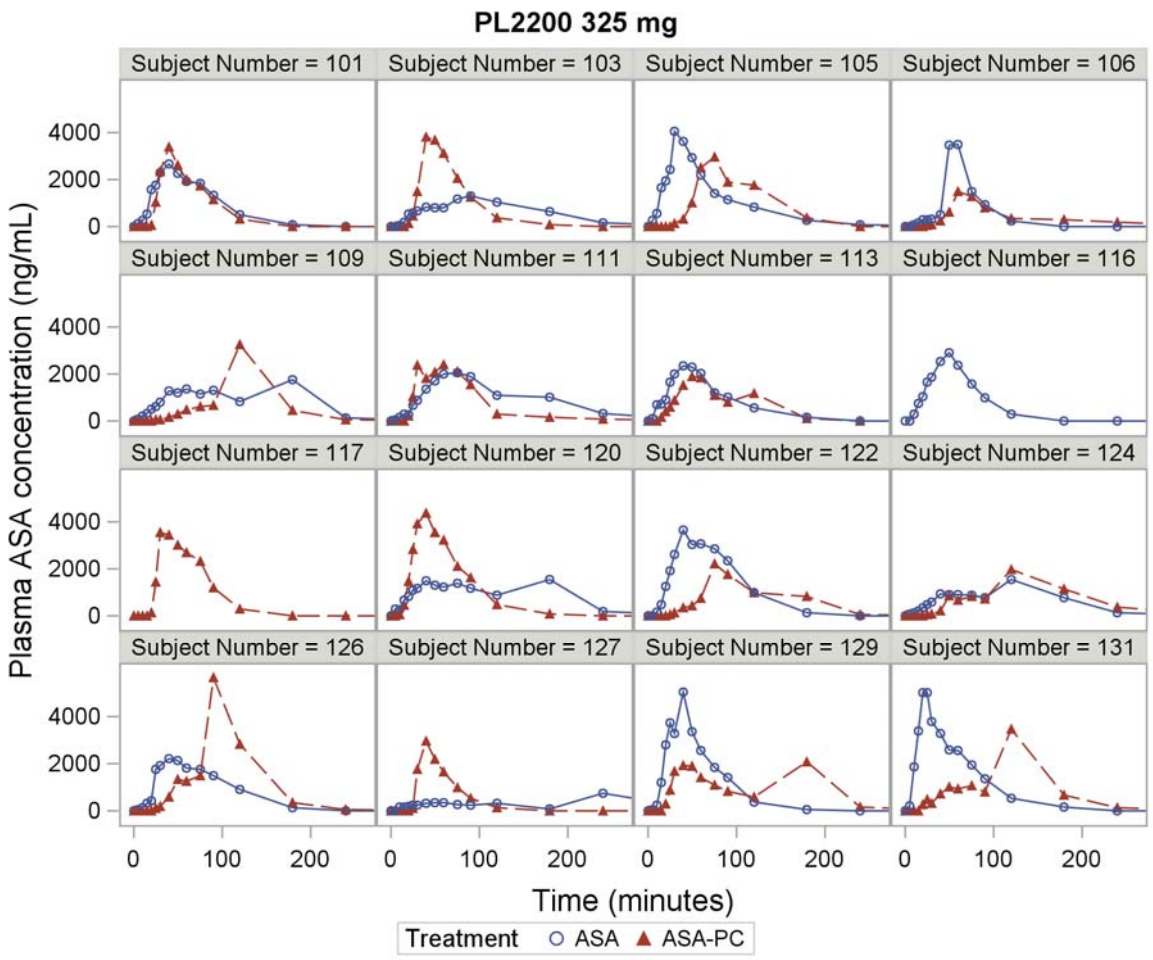


**Figure 4** Individual plasma concentration versus time profile following administration of ASA-PC (test, triangle) or ASA (reference, circle).

Note: (1) Subjects 116 and 117 were discontinued from the study before the second study period. Both subjects failed pre-dose AA induced platelet aggregation (2) Subject 126 was deemed an outlier by the sponsor based on analysis of residuals.

## Study PL-ASA-003 (Food effect)

| **Study Protocol #** PL-ASA-003 | **Study period** 10/23/2010 to 12/05/2010 |
|---|---|

**Title**

A randomized actively (sic) controlled cross-over food effect study of PL2200 in healthy volunteers.

**Objectives**

To assess the effect of standard high fat FDA recommended meal on the bioavailability of acetylsalicylic acid following administration of a single dose of PL2200 at the 650 mg dose level.

> *Reviewer's comment: Comparison of the effect of food on the bioavailability of acetylsalicylic acid was the secondary analysis in this study.*

**Study Design**

Open label, randomized, two period crossover study, with a minimum of 7 days of washout between study periods.

**Study medication**

| | |
|---|---|
| Dosage Form | PL2200 capsule |
| Dosage Strength | 325 mg |
| Batch #. | 13105.003A |
| Administration | oral |

**Sampling schedule**

Pharmacokinetics: Blood samples were collected for pharmacokinetic analysis at pre-dose, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90 minutes and 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose.

**Data Analysis Methods**

Summary statistics were calculated and presented for PK measures. ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

**Study population**

| | |
|---|---|
| Randomized/Completed/ Discontinued Due to AE | 20/20/0 |
| Age (SD) years | 36.8 (8.6) |
| Male/Female | 9/11 |
| Race (Caucasian/Black/Asian/Hispanic of latino/other) | 15/3/1/1 |

**Results:**

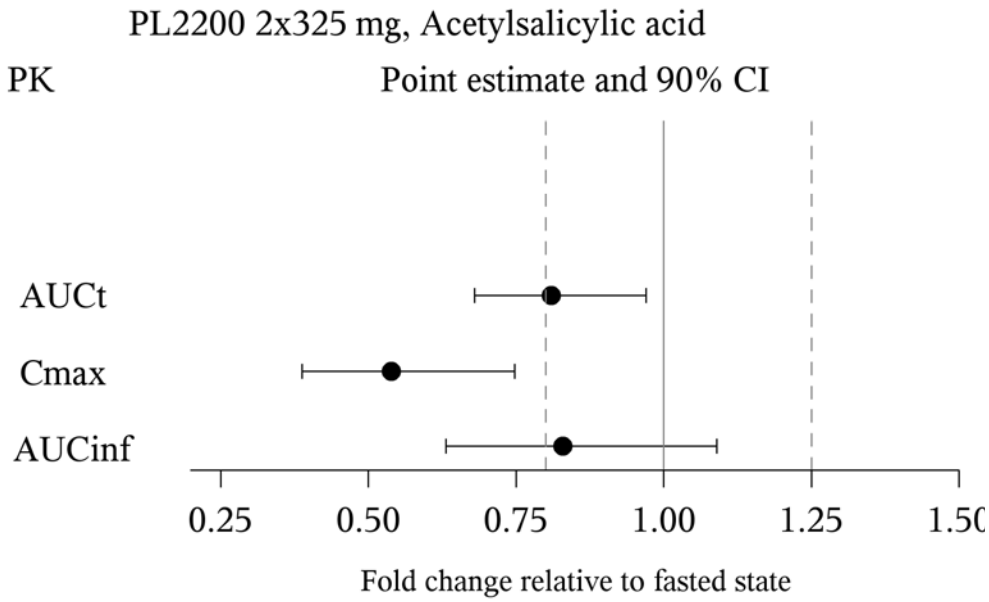


**Figure 5** Food decreases bioavailability of ASA following administration of PL2200. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean.

**Assay Method**

Acetylsalicylic acid was measured using validated HPLC-MS/MS method.

**Safety** Death/SAE: None

**Conclusion**

Food reduces bioavailability of acetylsalicylic acid following administration of PL2200.

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/s/

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DIVYA MENON ANDERSEN
11/13/2012

RAJANIKANTH MADABUSHI
11/14/2012

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

# Office of Clinical Pharmacology

## *New Drug Application Filing and Review Form*

***General Information About the Submission***

| | Information | | Information |
|---|---|---|---|
| **NDA/BLA Number** | ***NDA*-203697** | **Brand Name** | |
| **OCP Division (I, II, III, IV, V)** | ***II*** | **Generic Name** | ***Aspirin, 325 mg*** |
| **Medical Division** | ***DNCE*** | **Drug Class** | ***Salicylates*** |
| **OCP Reviewer** | ***Suresh B Naraharisetti*** | **Indication(s)** | ***OTC –Pain indications*** |
| **OCP Team Leader** | ***Yun Xu*** | **Dosage Form** | ***Immediate- release Capsule*** |
| **Pharmacometrics Reviewer** | | **Dosing Regimen** | |
| **Date of Submission** | | **Route of Administration** | ***Oral*** |
| **Estimated Due Date of OCP Review** | | **Sponsor** | **PLx Pharma** |
| **Medical Division Due Date** | | **Priority Classification** | |
| **PDUFA Due Date** | **January 14, 2013** | | |

### *Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | | | | |
| **Tabular Listing of All Human Studies** | | | | |
| **HPK Summary** | | | | |
| **Labeling** | | | | |
| **Reference Bioanalytical and Analytical Methods** | **X** | **1** | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | |
|---|---|---|---|---|
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD -** | | **2** | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | **X** | **1** | | **Pivotal BE study** |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | **X** | **1** | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | **Sponsor is requesting a waiver** |
| **Literature References** | | | | |
| **Total Number of Studies** | | **5** | | |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | X | | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | X | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | X | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | X | | | |
| 5 | Has a rationale for dose selection been submitted? | X | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | X | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | X | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | X | | | |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) | | | | | |
|---|---|---|---|---|---|
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | X | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | X | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | X | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | | | X | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**
**Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

***Comments to be communicated to the Sponsor in the Day-74 letter***

- ***After preliminary review for your data, it appears that after inclusion of all subjects in the BE analysis, your product failed to meet the BE criteria at both dose levels of 325 and 650 mg. Whether this is acceptable for approval of your NDA will be a review issue.***

- ***For 325 mg dose, you indicated that the upper limits of the 90% CI for both AUC and $C_{max}$ failed to meet the BE criteria because of the two influential outliers. Provide rationale for why these two subjects were considered as influential outliers, and reason leading to different PK exposure of these two subjects. Provide subject numbers of these two outliers as well as BE analysis results with and without these two subjects.***

- ***For 650 mg dose, you indicated subject 115 as an influential outlier and excluded this subject from BE analysis. In Section 16.1.13, Outlier Exclusion Summary, you showed that inclusion of this subject failed the BE criteria for lower limit of 90% CI for AUC. Provide plasma concentration-time data and PK parameters for this subject. Provide rationale why this subject should be excluded from the BE analysis, and reason leading to the different PK exposure of this subject. Provide BE analysis results with and without this subject.***

- ***Taking your product with food results in 22% lower Cmax in comparison to the fasted state. You indicated that this is consistent with results reported in the published literature on the effects of food on aspirin bioavailability of various dose forms, and with information provided in the 21 CFR 343 aspirin (internal analgesic) monograph. Whether the food effect result for your product is consistent with other Aspirin products will be a review issue.***

## BACKGROUND

PLx Pharma submitted a 505 (b) (2) NDA for PL 2200 as an immediate-release oral capsule consisting of aspirin, a non-steroidal anti-inflammatory drug, formulated in a lipid suspension of soybean-derived lecithin. Each capsule contains 325 mg of aspirin USP (active ingredient) and (b) (4) of soy lecithin. The product is being developed as an analgesic/antipyretic for over-the-counter (OTC) use. (b) (4)

PLx Pharma (PLx) is seeking the clinical indications for aspirin outlined in the Tentative Final Monograph for OTC internal analgesic products for oral administration: as a fever reducer and analgesic indicated for the temporary relief of headaches, muscle pain, toothache, pain and fever of colds, and minor pain of arthritis.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

As a 505(b) (2) NDA: Sponsor is relying on the Agency's findings on the safety and efficacy of aspirin. In support of this NDA, sponsor conducted the following Clinical Pharmacology/Clinical studies:

- Two PK studies in healthy volunteers
  - Pivotal Bioequivalence Study (PL-ASA-001):
    - A Randomized, Actively Controlled, Cross-Over Bioequivalence Study of PL2200 Versus Bayer Aspirin in Healthy Volunteers
  - Food-Effect Study (PL-ASA-003) :
    - A Randomized, Actively Controlled, Cross-Over Food-Effect Study of PL2200 in Healthy Volunteers

- One Safety study in healthy volunteers:
  - GI Safety Study: (PL-ASA-002):
    - A Randomized, Single-blind, Endoscopic Evaluation Of Upper GI Mucosal Damage Induced By Aspirin-PC (Pl2200) Versus Aspirin In Healthy Volunteers

The conducted PK studies meet the regulatory requirements for filing and this application is filable from the clinical pharmacology perspective. Additional details of the application and conducted clinical pharmacology studies can be found in the slides presented in the filing meeting dated 04/30/2012, attached to this tracking sheet. Based on the preliminary review, the above comments need to be communicated to the sponsor in 74-day letter.

| | |
|---|---|
| Suresh Babu Naraharisetti | May 3, 2012 |
| Reviewing Clinical Pharmacologist | Date |
| Xu Yun | May 3, 2012 |
| Team Leader/Supervisor | Date |

# Overview

| | |
|---|---|
| Application Type | 505 (b) (2) |
| Sponsor | PLx Pharma |
| Proposed Brand Name | (b) (4) |
| Generic Name | Aspirin- Acetyl Salicylic Acid |
| Formulation; Strengths | IR Capsules; 325 mg |
| Proposed Indications | Same as Monograph for OTC internal analgesic products for oral administration; Pain reliever/fever reducer<br>•fever reducer and analgesic indicated for the temporary relief of headaches, muscle pain, toothache, pain and fever of colds, and minor pain of arthritis. |
| Previous meetings | Pre IND: 2007 ; EOP2: 2009 ; PNDA: 2012 |

1

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www.fda.gov

# Background

- 505(b)(2) NDA: Relying on the Agency's findings on the safety and efficacy of aspirin
- Clinical Studies:
  - Efficacy Studies- None
  - Safety Studies- GI safety study (Aspirin PC versus Bayer Aspirin)
- Clinical Pharmacology Studies:
  - BE
  - Food Effect

2

# Bioequivalence Study (PL-ASA-001):

- A Randomized, Cross-Over BE Study of PL2200 Versus Bayer Aspirin in Healthy Volunteers
- BE was evaluated at two dose levels
  - 1 x 325 mg = 325 mg (PL2200 vs Bayer® Aspirin)
  - 2 x 325 mg = 650 mg (PL2200 vs Bayer® Aspirin)
- Healthy Volunteers; n=32; 2 weeks washout
- Primary Analyte for BE: Salicylic acid



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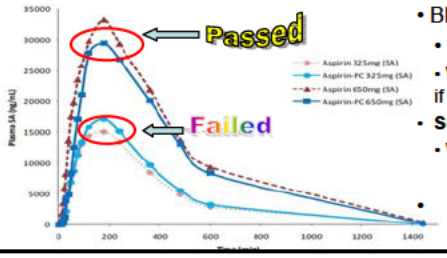
## Geometric Mean Ratios (PL2200 to Aspirin) of **Salicylic Acid** PK Parameters and 90% CI

| Parameter | 325 mg | | | 650 mg | | |
|---|---|---|---|---|---|---|
| | N | Ratio (%)[a] | 90% CI[b] | N | Ratio (%)[a] | 90% CI[b] |
| $AUC_{0-t}$ (ng × min/mL) | 14 | 110.56 | (95.58, 127.88) | 15 | 92.02 | (80.52, 105.17) |
| $AUC_{0-\infty}$ (ng × min/mL) | 14 | 111.39 | (96.67, 128.34) | 15 | 93.25 | (82.30, 105.65) |
| $C_{max}$ | 14 | 111.28 | (96.33, 128.56) | 15 | 99.55 | (87.92, 112.71) |

[a] Ratio = 100 x Geometric Mean (PL2200) / Geometric Mean (Aspirin)
[b] 90% Confidence Interval of the Ratio of PL2200 to Aspirin

- Thalf is ~2.5 hr




- BE failed at 325 mg level
  - Two subjects are influential outliers
  - Will be a review issue in day -74 letter, what is the resul if these subjects are excluded?)
- **Subject 115 is excluded from 650 mg BE analysis**
  - Will be further investigated during review

## Geometric Mean Ratios (PL2200 to Aspirin) of **Acetyl Salicylic Acid** PK Parameters and 90% CI

| Parameter | 325-mg Dose | | | 650-mg Dose | | |
|---|---|---|---|---|---|---|
| | n | Ratio (%)[a] | 90% CI[b] | n | Ratio (%)[a] | 90% CI[b] |
| $AUC_{0-t}$ (ng×min/mL) | 14 | 99.37% | (86.52, 114.13) | 16 | 84.12% | (74.63, 94.82) |
| $AUC_{0-\infty}$ (ng×min/mL) | 8 | 89.02% | (72.73, 108.96) | 11 | 82.59% | (72.81, 93.69) |
| $C_{MAX}$ (ng/mL) | 14 | **121.8%** | (83.62, 172.73) | 16 | 97.72% | (72.58, 13.57) |

a – Ratio = 100 × Geometric Mean (PL2200) / Geometric Mean (Aspirin)
b – 90% Confidence Interval of the Ratio of PL2200 to Aspirin

- Sponsor submitted results of ASA as well
- Failed BE for ASA (Note: BE is based on salicylic acid for Pain)

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# Food Effect

- Randomized,Cross-Over Food-Effect Study of PL2200 in Healthy Volunteers
- Treatments: 650 mg(2 x 325-mg hard capsules)
- Food: High-fat, high-caloric meal of 800-1000 calories (50% calories from fat)
- Washout 7 days
- N= 20

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# Food effect- PK

| PK Parameter[a] | Difference Between Log-Transformed Fed and Fasted States | Standard Error of Difference | Ratio of Fed to Fasted | 90% Confidence Interval | ANOVA CV (%) |
|---|---|---|---|---|---|
| $AUC_{0-t}$ ([µg x min]/mL) | -0.1212 | 0.0449 | 88.59 | (81.95, 95.76) | 14.27 |
| $AUC_{0-\infty}$ ([µg x min]/mL) | -0.1186 | 0.0449 | 88.81 | (82.17, 96.00) | 14.26 |
| $C_{max}$ (µg/mL) | -0.2512 | 0.0418 | 77.78 | (72.34, 83.63) | 13.29 |

a: n=20 for all PK parameters

- *Cmax is 22% lower; BE criteria of 80 to 125% fell out of the range for Cmax*
  - *Sponsor states that food effect on Aspirin bioavailability is consistent as reported* literature on the effects of food on aspirin bioavailability of various dose forms, and with information provided in the 21 CFR 343 aspirin (internal analgesic). monograph
    - *Will be included in 74 day letter as a review issue.*
- *Tmax is 1.7 hr delayed with food (4.7 hr with food versus 3 hr fasted)*

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# NDA 203697 – Aspirin Capsules

- Filable
- DSI consult form

**Mid-cycle deliverables:**

- Assessment of BE and Food Effect

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/s/

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SURESH B NARAHARISETTI
05/07/2012

YUN XU
05/08/2012