

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205103Orig1s000

PRODUCT QUALITY REVIEW(S)



Recommendation:

This 505(b)(2) application is recommended for Approval from the OPQ perspective with expiration dating period of 36 months.

**NDA 205103 (Resubmission)
Review #3**

Drug Name/Dosage Form	Yosprala™ (aspirin and omeprazole) delayed-release tablets
Strength	81 mg or 325 mg aspirin/ 40 mg omeprazole
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Aralez Pharmaceuticals R&D Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission Class 2	14-Mar-2016	All OPQ disciplines
<i>Amendment</i>	<i>28-Apr-2016</i>	<i>Drug Substance/Drug Product</i>
<i>Amendment</i>	<i>24-May-2016</i>	<i>Drug Product</i>
<i>Amendment</i>	<i>01-Jun-2016</i>	<i>Drug Substance</i>
<i>Amendment</i>	<i>10-Jun-2016</i>	<i>Drug Product</i>
<i>Amendment</i>	<i>24-Jun-2016</i>	<i>Drug Product</i>
<i>Amendment</i>	<i>29-Jun-2016</i>	<i>Labeling</i>

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xavier Ysern, Ph.D.	OMPT/CDER/OPQ/ONDP/D ND API/NDBII
Drug Product	Zhengfang Ge, Ph.D.	OMPT/CDER/OPQ/ONDP/D ND PII/BV
Process	Jingbo Xiao, Ph.D.	OMPT/CDER/OPQ/OPF/DIA/ IA/BII
Microbiology	Jingbo Xiao, Ph.D.	OMPT/CDER/OPQ/OPF/DIA/ IA/BII
Facility	Christina Capacci-Daniel, Ph.D.	OMPT/CDER/OPQ/OPF/DIA/ IA/BII
Biopharmaceutics	Hansong Chen, Ph.D.	CDER/OPQ/ONDP/DB II
Regulatory Business Process Manager	Truong Quach, Phar. D.	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI



QUALITY ASSESSMENT



Application Technical Lead	Danuta Gromek-Woods, Ph.D.	OMPT/CDER/OPQ/ONDP/D NDPII/BV
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue Jr.	OGROP/ORA/OO/OMPTO/D MPTPO/MDTP
Environmental Analysis (EA)	NA	NA

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	[Redacted]	(b) (4)	Adequate	Last review dated 07-Jun-2016	Drug substance in NDA 205103
	Type II			Adequate	last review dated 03-May-2016	Used to manufacture (b) (4) (DMF (b) (4))
	Type II			Adequate	last review dated 24-Feb-2016	Drug substance in NDA 205103

B. Other Documents: IND, RLD, or sister applications

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78747	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			

Proposed Indication(s) including Intended Patient Population	YOSPRALA is a combination of aspirin, an anti-platelet agent, and omeprazole, a proton pump inhibitor, indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.
Maximum Daily Dose	1 tablet daily
Route of Administration	Oral (delayed release tablets (aspirin: delayed release; omeprazole: immediate release))

Executive Summary

I. Recommendations and Conclusion on Approvability

This applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product before the drug administration.

The Office of Facility and Process has made a final overall “Approve” recommendation for the manufacturing inspection of facilities involved in this application.

Labeling and labels are deemed satisfactory from the CMC perspective.

The issue raised by the Biopharmaceutics Review about acid degradation of omeprazole in the stomach is deemed to be beyond the Biopharmaceutics’ purview and its safety concern is deferred to Clinical Team, but OPQ will support and cooperate with any post approval investigation on this issue, if it be warranted by the Clinical Team.

Therefore, from the OPQ perspective, this application is recommended for Approval with expiration dating period of 36 months.

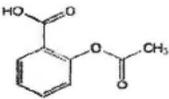
II. Summary of Quality Assessments

A. Product Overview

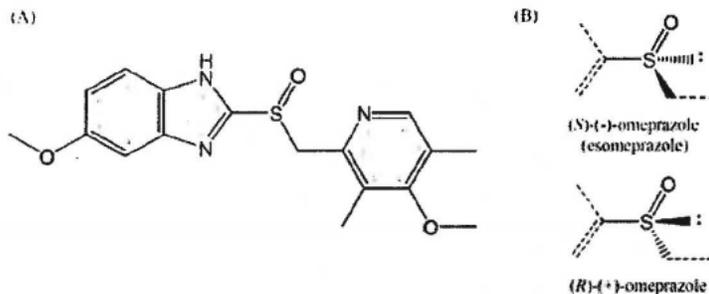
Aspirin and omeprazole are the two active pharmaceutical ingredients of the drug product Yosprala™ (81 mg or 325 mg aspirin/ 40 mg omeprazole) tablets. The proposed drug product is an aspirin delayed-release/omeprazole immediate-release tablet. The listed drugs for this 505(b)(2) application are Ecotrin® GSK (aspirin) and Prilosec® AstraZeneca (omeprazole), both are delayed-release.

Aspirin is provided (b) (4)

[Redacted text block]

Name	<i>Aspirin</i> <i>Aspirin, USP</i> <i>2-Acetoxybenzoic Acid</i>	(b) (4)
Structure		
MW (g/mol)	180.16	
Molecular Formula	C ₉ H ₈ O ₄	
CAS RN	50-78-2	

Omeprazole's chemical structure is shown below:



The stability of omeprazole in solution is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions. Omeprazole is a racemate of two enantiomers, as shown in the figure above.

The drug product manufacturing steps use (b) (4). The tablets for both strengths consist of an aspirin core that is coated with (b) (4) film coats, (b) (4) as shown below:



For detailed composition of (b) (4) film coats, please see the Drug Product section of this review.

B. Quality Assessment Overview

The drug substance reviewer, Dr. Xavier Ysern, concludes that the quality of “the described drug substances is deemed acceptable to support their use in the manufacture of the proposed drug product Yosprala™ (81 mg or 325 mg aspirin/ 40 mg omeprazole) tablets as described under Applicant’s NDA 205-103”.

As per Drug Product reviewer, the aspirin mixture supplied (b) (4) is supported by stability results for the drug product.

No significant differences have been observed for the real time stability results comparing the drug products using (b) (4) aspirin and drug products using (b) (4) aspirin (see review #2 in the previous review cycle). Therefore, the proposed 36 months expiration dating period is granted for the drug product stored at USP room temperature condition based on the 36 months long term stability data for the drug products manufactured with aspirin (b) (4). Post-approval stability protocol and commitment are adequate.

The Process Review states that there are no changes (b) (4) (b) (4) in the manufacturing and commercial packaging configurations for PA8140 tablets and PA32540, and the proposed change of batch sizes for the commercial production is deemed acceptable. The firm provided adequate information for in-process controls and for the commercial scale-up.

Regarding the Microbiology assessment, the review of the original submission dated 08-Jul-2013 remains adequate for microbial limit specifications for the drug product, as there are no changes in the control of microbial limits in the current resubmission.

Biopharmaceutics Review dated 9-Aug-2016 made a recommendation of approval, but raised a concern regarding the degradation of omeprazole in the acidic medium of stomach: As stated in the review,

“The dissolution of Yosprala tablet in acid medium (0.1 N HCl) demonstrated that

(b) (4)
”, see graph below:



However, in the addendum dated 17-Aug-2016 to the the previous Review (9-Aug-2016), Biopharmaceutics Team states that safety concern in-vivo about these degradants is beyond the Biopharmaceutics purview and is deferred to pre-clinical and clinical teams.

APPEARS THIS WAY ON ORIGINAL

The Office of Facility and Process has made a final overall manufacturing inspection “Approve” recommendation for the facilities involved in this application, as illustrated in the inspectional assessment report below:

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**

Assay, stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	L	Suitable analytical methodology, suitable container closure and storage conditions	Acceptable	
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	Suitable microbial release testing.	Acceptable	
Dissolution	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	M	Meeting the acceptance criterion of the approved dissolution test	Acceptable	
Degradation of unprotected omeprazole in stomach	PPIs are known for their chemical instability in acidic medium.	H	Degradation studies of omeprazole in the stomach, degradants characterization,	Acceptable from OPQ perspective, but will cooperate with OND, if further clinical or preclinical studies are warranted.	(b) (4) if it is determined that it will pose a significant safety concern on the patients.

Application Technical Lead:

Moo-Jhong Rhee, Ph.D.
Branch V/DNDP II/ONDP

Moojhong Rhee -S

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NDA 205103

Trade Name
(aspirin and omeprazole) delayed release tablets
81 mg (or 325 mg)/40 mg

POZEN Inc.

Zhengfang Ge, Ph. D.

Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

For

Division of Gastroenterology and In-Born Error Products



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Chemistry Review Data Sheet

1. NDA 205103
2. REVIEW #: 2
3. REVIEW DATE: Doc 9, 2014
4. REVIEWER: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	25-March-2013
Amendment	27-March-2013
Amendment	30-April-2013
Amendment	21-May-2013
Amendment	13-June-2013
Amendment	29-July-2013
Amendment	31-July-2013
Amendment	8-June-2013
Amendment	1-Aug-2013
Amendment	3-Oct-2013
Amendment	11-Nov-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	30-June-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Pozen Inc.

Address: 1414 Raleigh Rd, Suite 400



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Paul A. Ossi

Telephone: 919-913-1030

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): aspirin, omeprazole
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 4
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: secondary prevention of cardio and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers

11. DOSAGE FORM: Tablets (delayed release for aspirin, immediate release for omeprazole)

12. STRENGTH/POTENCY: aspirin/omeprazole 81 mg (or 325 mg)/40 mg per tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

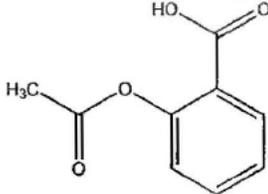
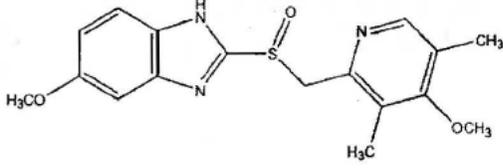
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Chemistry Review Data Sheet

<u>Aspirin</u> Chemical name: 2-Acetoxybenzoic Acid USAN: Aspirin CAS: 50-78-2	 $C_9H_8O_4$; 180.2 g/mol
<u>Omeprazole</u> Chemical name: (RS)-5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1Hbenzo[d]imidazole USAN: Omeprazole CAS: 73590-58-6	 $C_{17}H_{19}N_3O_3S$; 345.4 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	1-Aug-2013	
	II			1	Inadequate*	8-July-2013	* The DMF is found (b) (4) adequate for this NDA (see review #1.)
	IV			1	Adequate	19-June-2013	
	IV			1	Adequate	19-June-2013	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED RE-VIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
OC	Withhold	12/9/2014	C. Capacci-Daniel
Pharm/Tox	N/A		
Biopharm	Approval	Nov 25, 2014	B. Zolnik, PhD
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical Exclusion is claimed and is granted.		Zhengfang Ge, Ph.D.
Microbiology	Approval	July 8, 2013	Jessica G. Cole, PhD

Chemistry Assessment Section

The Chemistry Review for NDA 205103

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC Review #1 dated 24-April-2014 had noted the following pending issue:

21CFR 314.125(b)(13)

- the Office of Compliance issued an overall "**Withhold**" recommendation for the inspections of the manufacturing facilities.

And the Office of Compliance issued another overall "**Withhold**" recommendation for the facilities in this resubmission (see the **Attachment**), therefore, from the ONDQA perspective, this NDA is **not** recommended for approval in its present form per 21CFR 314.125(b)(13).

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

None

II. Summary of Chemistry Assessments

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

Drug Substance(s)

Aspirin, USP is supplied [REDACTED] (b) (4)

Omeprazole is manufactured [REDACTED] (b) (4)

See CMC Review #1 for other information.

Drug Products

PA32540 Tablets (325 mg aspirin/40 mg omeprazole) and PA8140 Tablets (81 mg aspirin/40 mg omeprazole) are oval, blue-green, film coated tablets with "325/40" or "81/40" printed in black on one side. The products are packaged with (b) (4) 30, 90 (b) (4) count configuration in white high density polyethylene (HDPE) bottle with a (b) (4) screw cap closure (b) (4)

Chemistry Assessment Section

(b) (4) All excipients are compendial (b) (4)
which were previously found acceptable.

The drug products will be manufactured (b) (4)

For the tablets of 325 mg aspirin and 40 mg omeprazole (PA32540), stability data obtained at the long term condition (25°C/60%RH) over 36 months and at accelerated condition over 6 months met the specification for the tablets stored in (b) (4) 30, 90 (b) (4) count HDPE bottles. No significant trends in stability data were observed for appearance, aspirin assay, omeprazole assay, aspirin dissolution and omeprazole dissolutions. The proposed expiration dating period of 36 months is acceptable based on the real time stability data.

For the tablets of 81 mg aspirin and 40 mg omeprazole (PA8140), stability data obtained at the long term condition (25°C/60%RH) over 12 months, and 6 months at the accelerated conditions (40°C/75%RH) for 6 months met specifications for all bottle packaging configurations (b) (4)
(b) (4)

(see the **Review #1** dated 11/21/13 for more detailed information)

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

See CMC Review #1

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(13)

- The Office of Compliance has issued an overall "**Withhold**" recommendation for the facilities involved in this resubmission (see the **Attachment**).

Chemistry Assessment Section**III. Administrative****A. Reviewer's Signature**

Zhengfang Ge, Ph.D.
Reviewer/ONDQA

Zhengfang Ge

-A

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Moo-Jhong Rhee, Ph.D.
Branch Chief/ONDQA

Moojhong Rhee -S

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B. Endorsement Block

Zhengfang Ge, Ph.D.
Reviewer/ONDQA

Moo-Jhong Rhee, Ph.D.
Branch Chief/ONDQA

Marie Kowblansky, Ph.D. CMC Lead/ONDQA

C. CC Block



Chemistry Assessment Section

IV. Attachments



Overall Manufacturing Inspection Recommendation

NDA 205103-Orig1-Resubmission/Class 2(36)

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Withhold

Facility Inspection - Overall Application Re-evaluation Date
3/3/15

NDA 205103 Biopharmaceutics Review

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 205103 (Re-submission)	Reviewer: Banu Sizanli Zolnik, Ph.D.	
Division:	Division of Gastroenterology and Inborn Errors Products		
Applicant:	Pozen	Acting Team Leader: Elsbeth Chikhale, Ph.D.	
Trade Name:	Yosprala	Acting Supervisor: Paul Seo, Ph.D.	
Generic Name, Strength:	Aspirin/Omeprazole, 81/40 mg, 325/40 mg Tablets	Date Assigned:	July 15, 2014
Indication:	Secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin associated gastric ulcers	Date of Review:	November 25, 2014
Formulation:	Modified Release Tables (bilayer IR/DR)	Route of Administration: Oral	
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates June 30, 2014 (Resubmission)		Date of informal/ Formal Consult	PDUFA and GRMP DATE
		NA	PDUFA date: 12/30/2014 GRPM date 12/2/2014
Type of Submission:	505 (b) (2) Application		
Key review points	NA		

EXECUTIVE SUMMARY

This is a resubmission of NDA 205103 which was issued a Complete Response (CR) action due to facility inspection related deficiencies.

In the Original Application, the Applicant, Pozen, submitted a 505(b)(2) NDA for Aspirin/Omeprazole 81/40 mg and Aspirin/Omeprazole 325/40 mg Tablets, indicated for use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin associated gastric ulcers. Both strength tablets consist of an aspirin pH sensitive delayed release core (b) (4) and an omeprazole coat with immediate release characteristics.

During the first cycle of the Biopharmaceutics Review, the dissolution method was found acceptable, however, the dissolution acceptance criteria for both strengths were found acceptable in an interim basis. (b) (4)

RECOMMENDATION

From the biopharmaceutics perspective, the original NDA was recommended for approval. In this submission, there are no new biopharmaceutics study/data included for review. Therefore, this Application is acceptable from the biopharmaceutics perspective; however note that there are two PMCs to be fulfilled.

Banu Sizanli Zolnik, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

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Zolnik -S

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Memorandum

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

Date: April 24, 2014

From: Zhengfang Ge, Ph.D.
CMC Reviewer, Branch IV
Division of New Drug Quality Assessment II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 205103

Subject: Final Recommendation

The CMC Review #1 dated 21-Nov-2013 had noted the following two pending issues:

1. 21CFR 314.125(b)(13)
 - Inspection of the manufacturing is pending overall recommendation from the Office of Compliance on the site acceptability.
2. 21 CFR 314.125(b)(1)
 - Drug product specification is not adequate pending resolution on dissolution test

And because of these deficiencies, in the CMC Review #1, this NDA was not recommended for approval from the ONDQA perspective.

On March 17, 2014, the Biopharm reviewer Dr. B. Zolnik concluded that the dissolution testing is acceptable on an interim basis for the current acceptance criteria for PA8140 and PA32540 Tablets and recommended Approval for the NDA. The drug product specification is now acceptable. (see **Attachment 1**, Drug Product Specification)

On April 24th, 2014, the Office of Compliance issued an overall “*Withhold*” recommendation for the inspections of the manufacturing facilities (see **Attachment 2**, EER Report).

In addition, the applicant submitted an amendment on Jan. 23, 2014. The amendment provided investigation

(b) (4)

(b) (4)

In the Executive Summary of the Drug Substance in Review #1, there is a typo for omeprazole. On page 8, I noted that [REDACTED] (b) (4) The word [REDACTED] (b) (4) is a mistake, and should be replaced with “omeprazole”.

Final Recommendation:

From the ONDQA perspective, this NDA is recommended for **Complete Response** per 21CFR 314.125(b)(13).

Attachment 1: Drug Product Specification

1. Specification for PA 8140 Tablets

Table 1: Quality Control Specifications

Test	Limit	Method
Appearance	Blue-Green, film-coated, oval tablet, printed with "81/40" in black on one side	P14100 - Visual inspection
Identification for Aspirin by HPLC/UV	Positive - The retention time for the aspirin peak is within (b)(4)% of the standard peak	929905 – HPLC/UV
Identification for Aspirin by FT-IR ^a	Positive	881700 – FT-IR
Assay for Aspirin by HPLC/UV	(b)(4)%	929905 – HPLC/UV
Uniformity of Dosage Units for Aspirin by HPLC/UV	Meets the requirements of the current USP	929905 – HPLC/UV
Related Substances for Aspirin by HPLC/UV	(b)(4) NMT (b)(4)% Individual NMT (b)(4)% Total NMT (b)(4)%	929905 – HPLC/UV
Identification for Omeprazole by HPLC/UV	Positive - The retention time for the omeprazole peak is within (b)(4)% of the standard peak	929906 – HPLC/UV
Identification for Omeprazole by TLC ^a	Positive	881600 - TLC
Assay for Omeprazole by HPLC/UV	(b)(4)%	929906 – HPLC/UV
Uniformity of Dosage Units for Omeprazole by HPLC/UV	Meets the requirements of the current USP	929906 – HPLC/UV
Related Substances for Omeprazole by HPLC/UV	Individual NMT (b)(4)% Total NMT (b)(4)%	929909 – HPLC/UV
Dissolution - Acid Resistance for Aspirin (0.1 N HCl)	Meets the requirements of the USP (NMT (b)(4)%)	929907 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm 120 minutes in 900 mL 0.1M hydrochloric acid at 37.0°C
Dissolution for Aspirin (pH 6.8)	Meets the requirements of the current USP (Q = (b)(4)% at (b)(4) minutes)	929907 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm 120 minutes in 900 mL 0.1M hydrochloric acid at 37.0°C followed by media replacement with 900 mL phosphate buffer pH 6.8 at 37.0°C
Dissolution for Omeprazole (pH 7.4)	Meets the requirements of the current USP (Q = (b)(4)% at (b)(4) minutes)	929908 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm Media - 900 mL phosphate buffer pH 7.4 at 37.0°C

^a Secondary test. Not tested routinely.

2. Specification for PA32540 Tablets

Table 1: Quality Control Specifications

Test	Limit	Method
Appearance	Blue-Green, film-coated, oval tablet, printed with "325/40" in black on one side	P14100 - Visual inspection
Identification for Aspirin by HPLC/UV	Positive - The retention time for the aspirin peak is within (b)(4)% of the standard peak	846520 – HPLC/UV
Identification for Aspirin by FT-IR ^a	Positive	881700 – FT-IR
Assay for Aspirin by HPLC/UV	(b)(4)%	846520 – HPLC/UV
Uniformity of Dosage Units for Aspirin by HPLC/UV	Meets the requirements of the current USP	846520 – HPLC/UV
Related Substances for Aspirin by HPLC/UV	(b)(4) NMT (b)(4)%	846520 – HPLC/UV
	Individual NMT %	
	Total NMT %	
Identification for Omeprazole by HPLC/UV	The retention time for the omeprazole peak is within (b)(4)% of the standard peak	846630 – HPLC/UV
Identification for Omeprazole by TLC ^a	Positive	881600 - TLC
Assay for Omeprazole by HPLC/UV	(b)(4)%	846630 – HPLC/UV
Uniformity of Dosage Units for Omeprazole by HPLC/UV	Meets the requirements of the current USP	846630 – HPLC/UV
Related Substances for Omeprazole by HPLC/UV	Individual NMT (b)(4)%	846720 – HPLC/UV
	Total NMT %	
Dissolution - Acid Resistance for Aspirin (0.1 N HCl)	Meets the requirements of the USP	883400 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm 120 minutes in 900 mL 0.1M hydrochloric acid at 37.0°C
Dissolution for Aspirin (pH 6.8)	Meets the requirements of the current USP (Q = (b)(4)% at (b)(4)minutes)	883400 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm 120 minutes in 900 mL 0.1M hydrochloric acid at 37.0°C followed by media replacement with 900 mL phosphate buffer pH 6.8 at 37.0°C
Dissolution for Omeprazole (pH 7.4)	Meets the requirements of the current USP (Q = (b)(4)% at (b)(4)minutes)	846330 – HPLC/UV USP dissolution Apparatus 1 (basket) at 100 rpm Media - 900 mL phosphate buffer pH 7.4 at 37.0°C

^a Secondary test. Not tested routinely.

Attachment 2: EER Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 205103/000	Sponsor:	POZEN INC
Org. Code:	180		1414 RALEIGH RD STE 400
Priority:	4		CHAPEL HILL, NC 275178834
Stamp Date:	25-MAR-2013	Brand Name:	YOSPRALA
PDUFA Date:	25-APR-2014	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	26-NOV-2013	Product Number; Dosage Form; Ingredient; Strengths	
		001; TABLET; OMEPRAZOLE; 40MG	
		001; TABLET; ASPIRIN; 81MG	
		002; TABLET; OMEPRAZOLE; 40MG	
		002; TABLET; ASPIRIN; 325MG	
FDA Contacts:	Z. GE	Prod Qual Reviewer	3017961358
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800) 3017963877
	S. BARLEY	Regulatory Project Mgr	3017962137
	M. KOWBLANSKY	Team Leader	3017961390

Overall Recommendation:	WITHHOLD	on 24-APR-2014	by C. CAPACCI-DANIEL ()	3017963532
	PENDING	on 02-MAY-2013	by EES_PROD	
	PENDING	on 02-MAY-2013	by EES_PROD	

Establishment:	CFN:	FEI:	(b) (4)	
			(b) (4)	
DMF No:				AADA:
Responsibilities:	DRUG SUBSTANCE LABELER			
	DRUG SUBSTANCE MANUFACTURER			
	DRUG SUBSTANCE OTHER TESTER			
	DRUG SUBSTANCE PACKAGER			
Profile:			(b) (4)	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION			
Milestone Date:	24-APR-2014			
Decision:	WITHHOLD			
Reason:	DISTRICT RECOMMENDATION			

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE LABELER
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE PACKAGER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

ZHENGFANG GE
04/24/2014

MOO JHONG RHEE
04/24/2014
Chief, Branch IV

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 205-103	Reviewer: Banu Sizanli Zolnik, Ph.D.	
Division:	Division of Gastroenterology and Inborn Errors Products		
Applicant:	Pozen	Secondary Signature: Sandra Suarez Sharp, Ph.D.	
Trade Name:	Yosprala PA8140 and PA32540	Acting Supervisor: Richard Lostritto, Ph.D.	
Generic Name, Strength:	Aspirin/Omeprazole, 81/40 mg, 325/40 mg Tablets	Date Assigned:	April 2, 2013
Indication:	Secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin associated gastric ulcers	Date of Review:	March 17, 2013
Formulation:	Modified Release Tables (bilayer IR/DR)	Route of Administration: Oral	
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates March 25, 2013 Original Application June 13, 2013 Seq. # 0005 July 31, 2013 Seq. # 0012 August 1, 2013 Seq. #0013 September 4, 2013 Seq. #0014 October 4, 2013 Seq. #0015 November 14, 2013 Seq. #0020 January 8, 2014 Seq. #0026 March 21, 2014 Seq.#0031		Date of informal/ Formal Consult	PDUFA DATE
		NA	April 25, 2014
Type of Submission:	505 (b) (2) Application		
Key review points	<ol style="list-style-type: none"> 1. Dissolution method and acceptance criteria 2. In vitro alcohol dose dumping studies 3. The data supporting appropriate bridging across the phases of formulations to the To-be-Marketed Formulation 		

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D) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission:

The Applicant, Pozen, submitted NDA 205-103 via 505(b)(2) NDA application for Aspirin/Omeprazole 81/40 mg (PA8140) and Aspirin/Omeprazole 325/40 mg Tablets (PA 32540) tablets for use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin associated gastric ulcers. Both PA32540 and PA8140 Tablets consist of an aspirin core with delayed release dependent pH (b) (4) and omeprazole coat with immediate release characteristics. It should be noted that omeprazole degrades rapidly in the gastric media.

The clinical development program for the proposed product included mainly the PA32540 Tablets. The Applicant conducted several BA/BE studies bridging the aspirin and omeprazole components (PA32540-104, -113, -115) to the respective listed drugs Ecotrin® (aspirin) and Prilosec® (delayed release omeprazole). These studies are being evaluated by the Office of Clinical Pharmacology (OCP) reviewer. Some minor manufacturing changes were implemented to the clinical safety and efficacy trial formulation (Phase 3/BE formulation). In support of these changes, appropriate bridging studies i.e. dissolution profile comparisons between the Phase 3/BE formulation to the To-be-Marketed (TBM) formulation for aspirin and omeprazole components for the PA32540 were submitted and found acceptable.

(b) (4)
To support the approval of the lower strength, the Applicant conducted BA/BE studies for aspirin (PA8140-102) and omeprazole (PA8140-103) bridging it to the Ecotrin 81 mg, and PA32540 Tablets, respectively. These studies are being evaluated by OCP reviewer.

Review:

This review focuses on the evaluation of: **1)** The acceptability of the dissolution method and acceptance criteria; **2)** The in vitro alcohol dose dumping studies; **3)** The data supporting appropriate bridging across the phases of development to TBM Formulation.

Reviewer Comments:

1) Dissolution Method and Acceptance Criteria

The following dissolution methods have been found acceptable for the aspirin and omeprazole components of the proposed drug product. The Applicant submitted sufficient information to support the discriminating ability of these methods.

Dissolution Method: Aspirin					
Stage	USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
Acid Resistance Stage *	USP I (basket)	100 rpm	900 mL	37°C ± 0.5°C	0.1 N HCl
Buffer Stage	USP I (basket)	100 rpm	900 mL	37°C ± 0.5°C	pH 6.8 Phosphate Buffer

Note:

(b) (4)

Dissolution Method: Omeprazole				
USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP I (basket)	100 rpm	900 mL	37°C ± 0.5°C	0.05 M Phosphate Buffer (pH 7.4)

Acceptance Criteria

The following acceptance criteria for PA 8140 and PA32540 Tablets are acceptable on an interim basis. The Applicant proposes

(b) (4)

Interim Dissolution Acceptance criteria for Aspirin PA8140 Tablets	
Acid Resistance Stage	81/40 mg: NMT (b) (4)% in 2 hours
Buffer Stage	81/40 mg: (b) (4)% in 45 minutes
Interim Dissolution Acceptance Criterion for Omeprazole for PA 8140 Tablets	
81/40 mg: (b) (4)% in 60 minutes	

Interim Dissolution Acceptance criteria for Aspirin PA325/40 Tablets	
Acid Resistance Stage	325/40 mg: NMT (b) (4)% in 2 hours
Buffer Stage	325/40 mg: (b) (4)% in 60 minutes
Dissolution Acceptance Criterion for Omeprazole for PA 325/40	
325/40 mg: (b) (4)% in 45 minutes	

The concern on the acceptance criteria was mainly with the aspirin component. A middle ground agreement (as shown in the above table) was reached for the buffer stage criteria on a teleconference with Applicant dated Dec 12, 2013. The Applicant believes that even the agreed upon interim criteria for the aspirin component is tight. The rationale behind the acceptability of the dissolution acceptance criteria on an interim basis is that we consider the proposed drug product, a low risk drug product for the aspirin component since 1) aspirin is considered a highly soluble and highly permeable substance¹ and 2) the dose-response curve for aspirin has been shown to be flat in dosages greater than 50 mg.

2) *The In Vitro Alcohol Dose Dumping*

In vitro dose dumping at the 40% alcohol level was observed for both PA 8140 and PA 32540. These findings were communicated to the clinical and clinical pharmacology review teams at the Mid-Cycle meeting on September 23, 2013 for further evaluation on the clinical impact of these results.

3) *Data Supporting Appropriate Bridging Across Phases of Drug Development*

PA 8140 Tablets:

A clinical PD study conducted with the Phase I formulation was initially proposed to support the approval of this strength. This study evaluated the effects on the gastro duodenal mucosa of PA8140. Major manufacturing changes including formulation and site changes were implemented to this Phase I formulation. A PK/BA study was conducted with the TBM formulation to support this change; however, this PK study only measured the acetyl salicylic acid component of the formulation. The review team was informed during the filing meeting that (b) (4) dissolution profile comparisons are not appropriate (b) (4) and could not be used to support the approval of this strength. Therefore, during the review cycle the Applicant was advised to conduct a BA/PK study to support the approval of this strength. In response to this recommendation, the Applicant submitted Study PA8140-103 which evaluated the PK and relative BA for the omeprazole component linking the TBM Formulation of the PA8140 and PA32540 Tablets. This study has been reviewed by the OCP review team.

PA32540 Tablets:

The pivotal efficacy and safety trials were conducted with a formulation that is similar to the TBM formulation. Specifically, there was a formulation change (b) (4) implemented to the Phase 3 and BE batches. This change is considered minor by the ONDQA-CMC review team. This change is supported by comparative dissolution testing. (b) (4)

The multivariate analysis conducted by the Applicant showed that the dissolution profiles for all Phase 3 and BE batches are similar to the TBM formulation. These results were confirmed by the Biopharmaceutics review team's multivariate analysis of the data. The 95% confidence intervals for the difference in dissolution at each time point and MANOVA analysis indicate similarity between the profiles compared. Therefore, the proposed change (b) (4) is acceptable.

¹ [J Pharm Sci](#). 2012 Aug;101(8):2653-67. doi: 10.1002/jps.23212. Epub 2012 Jun 6

II) RECOMMENDATION

From ONDQA-Biopharmaceutics perspective, NDA 205-103 for Aspirin/Omeprazole Tablets, 81 mg/40 mg and 325 mg/40 mg is recommended for **APPROVAL**. The dissolution method is found acceptable; however the acceptance criteria for PA8140 and PA32540 Tablets are found acceptable **on an interim basis** as stated above.

Banu Sizanli Zolnik, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Secondary Signature
Office of New Drug Quality Assessment

III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

1 What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

a. Drug Substance

Aspirin

Aspirin, USP is a white needle-like crystal or white crystalline powder that is slightly soluble in water, soluble in diethyl ether, chloroform, ethyl acetate, and readily soluble in ethanol. The pKa of aspirin is 1.8 (acidic) and hence solubility increases with increasing pH.

Omeprazole

Omeprazole, USP is a white to off-white powder. The pKa of the benzimidazole and pyridinium moieties are 8.8 (basic) and 4.0 (acidic) respectively. Omeprazole is practically insoluble in water and its solubility is dependent on the pH of the solution.

Below comment was conveyed to the Applicant with the 74-day filing review dated 5/23/2013:

- *Provide solubility data for the drug substance covering the physiological pH range.*

The Applicant's response in an amendment Seq. 005 dated 6/13/2013:

RESPONSE:



Reviewer's Comments to Applicant's Response provided in an amendment dated June 13, 2013 - SATISFACTORY

Aspirin Component: The solubility of aspirin in the proposed dissolution media of pH 6.8 Phosphate Buffer is expected to be between (b) (4) mg/mL based on the response provided by the Applicant above. The concentration of highest strength aspirin (325 mg) in 900 mL buffer is (b) (4) mg/mL, and therefore sink conditions are maintained for aspirin in the proposed dissolution method.

Omeprazole Component: The solubility of omeprazole in the proposed dissolution media of pH 7.4 0.05 M Phosphate Buffer is approximately (b) (4) mg/mL, and the concentration of the highest strength of omeprazole in 900 mL buffer is (b) (4) mg/mL, (b) (4) therefore sink conditions are maintained for omeprazole in the proposed dissolution method.

b. Drug Product



Figure 1: Schematic of PA32540 and PA8140 Tablet (not to scale)



Reviewer's Comment:

(b) (4)

- 2 Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?**

There is no information regarding BCS classification in the submission.

B) DISSOLUTION INFORMATION

B.1. DISSOLUTION METHOD

- 3 What is the proposed dissolution method?**

The dissolution method proposed as a quality control test for the aspirin and omeprazole components of the proposed drug product are summarized below:

Proposed Dissolution Method Aspirin					
Stage	USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
Acid Resistance Stage *	USP I (basket)	100 rpm	900 mL	37°C ±0.5°C	0.1 N HCl
Buffer Stage	USP I (basket)	100 rpm	900 mL	37°C ±0.5°C	pH 6.8 Phosphate Buffer

Note: (b) (4)

Proposed Dissolution Method Omeprazole				
USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP I (basket)	100 rpm	900 mL	37°C ±0.5°C	0.05 M Phosphate Buffer (pH 7.4)**

** (b) (4)

4 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

a. Selection of Dissolution Media



(b) (4)

(b) (4)



b. Selection of Dissolution Apparatus and Agitation Speed

(b) (4)



5 What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

The Applicant provided sufficient information to support the validity of the analytical methods for dissolution testing of the aspirin and omeprazole components of the proposed product. (Refer to CMC review and bioanalytical report at <\\cdsesub1\evsprod\nda205103\0000\m3\32-body-data\32p-drug-prod\active-tablet-all-01\32p5-contr-drug-prod\32p53-val-analyt-proc\32p53-dp-val-analyt-proc-8140.pdf> and <\\cdsesub1\evsprod\nda205103\0000\m3\32-body-data\32p-drug-prod\active-tablet-all-01\32p5-contr-drug-prod\32p53-val-analyt-proc\32p53-dp-val-analyt-proc-32540.pdf> for more details)

6 What data are available to support the discriminating power of the method?

In the original submission, the Applicant did not provide data to support discriminating capability of the proposed methods for aspirin and omeprazole. Therefore, the comments below were conveyed to the Applicant with the 74-day filing review dated 5/23/2013.

- ***Provide data supporting the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.). In addition, if available, submit data***

showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

Reviewer's Comments to Applicant's Response provided in an amendment S0005 dated June 13, 2013:

The Applicant has utilized the following approach to support the discriminating ability of the proposed method:

1) [REDACTED] (b) (4)

2) [REDACTED] (b) (4)

3) Omeprazole drug release was compared between two strengths.

1) [REDACTED] (b) (4)

[REDACTED] (b) (4)

Reviewer's Comment:

[REDACTED] (b) (4)

(b) (4)



(b) (4)



Reviewer's Comment:

The proposed dissolution method was able to distinguish aspirin release from PA32540 strength

(b) (4)



For further details refer to CMC review.

2)

(b) (4)

(b) (4)

Reviewer's Comment:

 (b) (4)
IR letter dated July 25, 2013 is conveyed to the Applicant to address this deficiency.

3) Omeprazole drug release was compared between PA 8140 and PA32540 strengths



Figure 9: Omeprazole release from PA 8140 and PA 32540 Tablets

Reviewer's Comment:

The Applicant compared omeprazole release from PA8140 and PA32540 strengths
 (b) (4)

Reviewer's comment conveyed to the Applicant in the IR letter dated July 25, 2013.

- *You have not provided adequate data to support the discriminating capability of the dissolution method for the Omeprazole component of your product for the PA8140 strength. As a reminder, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions*

vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.).

The Reviewer's Comment to the Applicant's response an amendment S-0014 dated September 4, 2013 –NOT SATISFACTORY

The Applicant submitted dissolution data [REDACTED] (b) (4)

This approach is found **unacceptable** [REDACTED] (b) (4)
[REDACTED] as it is clearly seen from the dissolution profiles shown below.

[REDACTED] (b) (4)

Reviewer's Comment on the Applicant's Response in an email dated September 26, 2013 for the FDA's teleconference comments- SATISFACTORY

The Applicant stated [REDACTED] (b) (4)

The Applicant also stated [REDACTED] (b) (4)

The reviewer agrees with the Applicant's justification for the omeprazole dissolution method [REDACTED] (b) (4)

7 Is the proposed dissolution method bio-relevant? What data are available to support this claim?

There were no data in the submission to help in the assessment of the bio-relevancy of the method (e.g. the ability of the method to reject batches that are not bioequivalent). The proposed dissolution method will be used as a quality control tool for release and stability.

8 Is the proposed method acceptable? If not, what are the deficiencies?

The Applicant provided adequate information to support the acceptability and discriminating power of the proposed dissolution method (b) (4)

B.2. ACCEPTANCE CRITERIA

9 What are the proposed dissolution acceptance criteria for this product?

The originally proposed acceptance criteria are:

Proposed Dissolution Acceptance Criteria for Aspirin	
Acid Resistance Stage	81/40 mg: NMT (b) (4)% 325/40mg: NMT %
Buffer Stage	81/40 mg: (b) (4)% in (b) (4) minutes 325/40mg % in (b) (4) minutes

Proposed Dissolution Acceptance Criterion for Omeprazole	
81/40 mg:	(b) (4)% in (b) (4) minutes
325/40mg:	% in 45 minutes

10 What data are available to support these criteria?

The Applicant stated that the proposed acceptance criteria was selected because it was found suitable for quality control and ensured the batch- to- batch quality. The data used to set the acceptance criteria is based on batches tested in pivotal clinical trials, and on release and stability batches.

11 Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?

The originally proposed acceptance criteria were permissive and therefore, it is found **NOT** acceptable.

PA 8140 Acceptance Criteria for Aspirin and Omeprazole

The dissolution profiles of all the clinical batches should be considered in setting the Acceptance Criteria for PA 8140. Therefore, in response to the filing communication, the Applicant provided the missing PA 8140 batch 3078656R dissolution data.



Figure 11 (left) and Figure 12 (right): Aspirin (left) and omeprazole (right) release from PA 8140 Primary Stability Batches

Reviewer's Comment:

ONDQA-Biopharmaceutics team proposed the below acceptance criteria for PA 8140 Tablets based on the dissolution data from the registration stability batches, and discriminatory capability of the dissolution method as discussed under the Section 6a. During a t-con with the Applicant, ONDQA-Biopharmaceutics team emphasized that the dissolution acceptance criteria should be set based on the mean values and therefore, it should be recognized that some batches may require Stage 2 and occasionally Stage 3 testing.

PA 8140 Tablets

Aspirin

Acid Stage: NMT (b) (4) % in 2 hr.

Buffer Stage: (b) (4)

$Q = \frac{w}{(4)} \% \text{ in } \frac{w}{(4)} \text{ minutes}$

Omeprazole

$Q = \frac{(b)}{(4)} \% \text{ in } 60 \text{ minutes}$

*In response to the concerns raised during a t-con with the Applicant on December 17, 2013, amendment S0026 was submitted on January 8, 2014, in which the Applicant proposed the following acceptance criteria on an **interim basis**.*

Applicant's proposal (b) (4)

*(b) (4) is found **acceptable**. ONDQA-Biopharmaceutics team agrees to accept the interim dissolution specifications. Interim Specification*

Agreement states that the Applicant agrees (b) (4)
 It should be noted that the Applicant accepted the acceptance criteria for acid resistance stage.

Interim Dissolution Acceptance criteria for Aspirin PA8140 Tablets	
Acid Resistance Stage	81/40 mg: NMT (b) (4)% in 2 hours
Buffer Stage	81/40 mg: (b) (4)% in 45 minutes
Interim Dissolution Acceptance Criterion for Omeprazole for PA 8140 Tablets	
81/40 mg: (b) (4)% in 60 minutes	

PA 32540 Acceptance Criteria for Aspirin and Omeprazole



Figure 13 (left) and Figure 14 (right): Aspirin (left) and omeprazole (right) release from PA 32540 Clinical and Primary Stability Batches

Reviewer's Comment:

Based on the dissolution data from the clinical, registration stability batches and discriminatory capability of the dissolution method as discussed under the Section 6b below acceptance criteria is recommended to the Applicant:

PA 325/40 Tablets

Aspirin

Acid Stage: NMT (b) (4)% in 2 hr.

Buffer Stage: (b) (4)

Q= (b) (4)% in (b) (4) minutes

Omeprazole

Q= (b) (4)% in 45 minutes

Similar to PA8140 tablets, the Applicant proposed (b) (4) and change the aspirin buffer stage acceptance criterion to $Q = \frac{w}{(4)}\%$ in 60 minutes for an interim basis in an amendment S0026 dated January 8, 2014. The Applicant's proposal (b) (4) is found acceptable (b) (4)

(b) (4) ONDQA-Biopharmaceutics team agrees on an interim acceptance criterion for aspirin buffer stage dissolution. (b) (4)

(b) (4) Note that the Applicant accepted the dissolution acceptance criterion for omeprazole for PA325/40 Tablets.

Interim Dissolution Acceptance criteria for Aspirin PA325/40 Tablets	
Acid Resistance Stage	325/40 mg: NMT $\frac{(b)}{(4)}\%$ in 2 hours
Buffer Stage	325/40 mg: $\frac{(b)}{(4)}\%$ in 60 minutes
Agreed Dissolution Acceptance Criterion for Omeprazole for PA 325/40	
325/40 mg: $\frac{(b)}{(4)}\%$ in 45 minutes	

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES



D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

- 16 Is there a request for a waiver of the submission of in vivo BE data (Biowaiver)? What is the purpose of the biowaiver request?**

There is no biowaiver request.

- 17 Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data is provided to support the acceptability of the IVIVC?**

There is no IVIVC information submitted.

D.2 SURROGATES IN LIEU OF DISSOLUTION

- 18 Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?**

No

D.3 DISSOLUTION AND QBD

- 19 If the application contains QbD elements, is dissolution identified as a CQA for defining design space?**

No

- 20 Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?**

Not Applicable (NA)

- 21. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?**

NA

- 22. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?**

NA

- 23. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?**

NA

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/s/

BANU S ZOLNIK
03/21/2014

SANDRA SUAREZ
03/21/2014

NDA 205103

Trade Name
(aspirin and omeprazole) delayed release tablets
81 mg (or 325 mg)/40 mg

POZEN Inc.

Zhengfang Ge, Ph. D.

Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

For
Division of Gastroenterology and In-Born Error Products

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Chemistry Review Data Sheet

1. NDA 205103

2. REVIEW #: 1

3. REVIEW DATE: Nov 21, 2013

4. REVIEWER: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

25-March-2013

Amendment

27-March-2013

Amendment

30-April-2013

Amendment

21-May-2013

Amendment

13-June-2013

Amendment

18-June-2013

Amendment

29-July-2013

Amendment

31-July-2013

Amendment

1-Aug-2013

Amendment

3-Oct-2013

Amendment

11-Nov-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Pozen Inc.

Address: 1414 Raleigh Rd, Suite 400

Representative: Paul A. Ossi

Telephone: 919-913-1030

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): aspirin, omeprazole
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 4
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: secondary prevention of cardio and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers

11. DOSAGE FORM: Tablets (delayed release for aspirin, immediate release for omeprazole)

12. STRENGTH/POTENCY: aspirin/omeprazole 81 mg (or 325 mg)/40 mg per tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

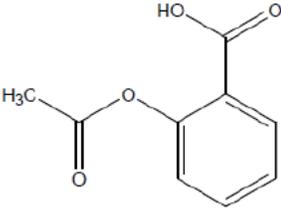
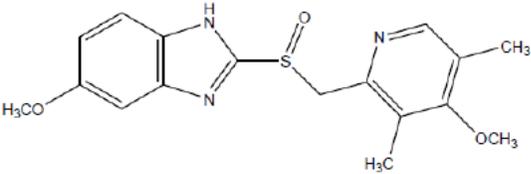
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

Chemistry Review Data Sheet

<u>Aspirin</u> Chemical name: 2-Acetoxybenzoic Acid USAN: Aspirin CAS: 50-78-2	 <p style="text-align: center;">$C_9H_8O_4$; 180.2 g/mol</p>
<u>Omeprazole</u> Chemical name: (RS)-5-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1Hbenzo[d]imidazole USAN: Omeprazole CAS: 73590-58-6	 <p style="text-align: center;">$C_{17}H_{19}N_3O_3S$; 345.4 g/mol</p>

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	1-Aug-2013	
	II		1	Inadequate*	8-July-2013	* The DMF is found (b) (4) adequate for this NDA (see review in section S.4.1.)	
	IV		1	Adequate	19-June-2013		
	IV		1	Adequate	19-June-2013		

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED RE-VIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	N/A		
Biopharm	pending		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical Exclusion is claimed and is granted.		Zhengfang Ge, Ph.D.
Microbiology	Approval	July 8, 2013	Jessica G. Cole, PhD

The Chemistry Review for NDA 205103

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has *not* provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has *not* issued an overall “Acceptable” recommendation for the facilities involved in this applicant.

The label/labeling issues are resolved satisfactorily.

Because of above two pending issues, from the ONDQA perspective, this NDA is *not ready* for approval in its present form per 21 CFR 314.125(b)(1) and (13) until these issues are satisfactorily resolved.

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

None

II. Summary of Chemistry Assessments

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

Drug Substance(s)

Aspirin, USP is supplied (b) (4)

The drug substance, aspirin (b) (4) is tested upon receipt by the drug product manufacturer (b) (4). All the other information is cross-referenced to DMF (b) (4). The most recent review of this DMF (b) (4) concluded that the DMF (b) (4) is inadequate (b) (4).

However, since the HPLC method described in this application for the assay and related substances is adequately validated and testing of the specified related substances and unspecified individual impurities are based on the current USP monograph and ICH Q3A, respectively, the deficiencies identified for the DMF are not deemed applicable to this NDA. The information on the drug substance aspirin (b) (4) is adequate.

Omeprazole is manufactured (b) (4). The drug substance, omeprazole is also tested upon receipt by the drug product manufacturer (b) (4).

Chemistry Assessment Section

(b) (4) The part of information (b) (4) submitted in the NDA is adequate. All other information is cross-referenced to DMF (b) (4), which is reviewed separately and found adequate to support this NDA.

Drug Products

PA32540 Tablets (325 mg aspirin/40 mg omeprazole) and PA8140 Tablets (81 mg aspirin/40 mg omeprazole) are oval, blue-green, film coated tablets with “325/40” or “81/40” printed in black on one side. The products are packaged with (b) (4) 30, 90 (b) (4) count configuration in white high density polyethylene (HDPE) bottle with a (b) (4) screw cap closure (b) (4)

(b) (4) All excipients are compendial (b) (4) which are also found acceptable during the review.

The tablets for both strengths consist of an aspirin core that is coated with (b) (4) film coat (b) (4)

PA32540 tablets were used in phase 1 and phase 3 studies. Except minor modification, the formulation of PA32540 is the same for the phase 3 and commercial product. (b) (4)

PA8140 tablets were only used in phase 1 clinical studies. The formulation of PA8140 used in phase 1 study is different from the commercial formulation.

The drug products will be manufactured (b) (4) Critical quality attributes are identified and controlled (b) (4) The drug product specification includes identification tests for both aspirin and omeprazole, HPLC assay for the actives, dosage uniformity (per USP), testing for aspirin and omeprazole related substances, dissolution testing (acid resistance, aspirin dissolution, omeprazole dissolution). The adequacy of the specification is pending satisfactory resolution of dissolution test and acceptance criteria (Biopharm Review is pending as of this review). Microbiology review has been conducted and recommended for “Approval” by Dr. J. Cole.

For the tablets of 325 mg aspirin and 40 mg omeprazole (PA32540), stability data obtained at the long term condition (25°C/60%RH) over 36 months and at accelerated condition over 6 months met the specification for the tablets stored in (b) (4) 30, 90 (b) (4) count HDPE bottles. No significant trends in stability data were observed for appearance, aspirin assay, omeprazole assay, aspirin dissolution and omeprazole dissolutions (b) (4) but still well within the specification. The stability data are consistent between the batches in the same package configurations for both active components in the drug products. The proposed expiration dating period of 36 months is acceptable based on the real time stability data.

For the tablets of 81 mg aspirin and 40 mg omeprazole (PA8140), stability data obtained at the long term condition (25°C/60%RH) over 12 months met the specification for the tablets stored in (b) (4) 30, 90 (b) (4) count HDPE bottles. Tablets stored at the accelerated conditions (40°C/75%RH) for 6 months met specifications for all bottle packaging configuration (b) (4)

Chemistry Assessment Section

(b) (4)
Based on the review of the stability data, 24 months expiration dating period can be granted for the PA8140 tablets packaged in 30, 90 (b) (4) count HDPE bottles (b) (4)

The applicant has accepted the Agency's request to display the drug product name and dosage form on the labels as Trade Name (aspirin and omeprazole) delayed release tablets based on the precedence of NDA 22511, an approved drug product with name and dosage form as Vimovo (naproxen and esomeprazole magnesium) delayed release tablets in which naproxen is immediate release and esomeprazole magnesium is delayed release. The revised labeling/labels are adequate from the CMC perspective.

The Office of Compliance has *not* issued an overall "Acceptable" recommendation for the facilities involved in this applicant.

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

BRANDNAME Tablets are indicated for patients (b) (4)

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(1)

- The submitted information does not assure the (identity, strength, purity, or quality, or any combinations) because of the following reason:
 - Drug product specification is not adequate pending resolution on dissolution test

21 CFR 314.125 (b)(13)

- The Office of Compliance has not issued an overall "Acceptable" recommendation for the facilities involved in this applicant.

(see the **List of Deficiencies** on p. 90)

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemistry Assessment Section

Zhengfang Ge, Ph.D.
Reviewer/ONDQA

Moo-Jhong Rhee, Ph.D.
Branch Chief/ONDQA

C. CC Block

Marie Kowblansky, Ph.D. CMC Lead/ONDQA

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/s/

ZHENGFANG GE
11/21/2013

MOO JHONG RHEE
11/21/2013
Chief, Branch IV

MEMORANDUM



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

DATE: 08 July 2013

TO: NDA 205103

FROM: Jessica G. Cole, PhD
CDER/OPS/NDMS Microbiology Reviewer

THROUGH: Bryan Riley, PhD
CDER/OPS/NDMS Microbiology Team Lead

cc: Stacy Barley
CDER/OND/DGIEP Project Manager

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for
“PA8140 and PA32540” [Submission Date: 25 March 2013]

The Microbial Limits specification for “PA8140 and PA32540” is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

PA8140 and PA32540 are film-coated tablets for oral administration. The aspirin core of the tablet is delayed release and the omeprazole is immediate release. [REDACTED] (b) (4)

[REDACTED] No microbiological in-process or release tests are proposed. The aspirin has a microbial limit of NMT [REDACTED] (b) (4) CFU/g total aerobic microbial count (TAMC) and NMT 100 CFU/g total yeast and mold count (TYMC) and the absence of *Escherichia coli*. There is no limit for omeprazole.

The following information request (in bold) was sent to the OND project manager on 16 May 2013 and a response was received from the applicant on 13 June 2013.

Microbiology Comment:

You propose to waive microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.

- 1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.**

MEMORANDUM

- a. Address how the (b) (4) are controlled for microbial growth (b) (4)
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at control points.
4. Provide an updated stability schedule to reflect microbial limits testing (b) (4)

Summary of the applicant's response:

The applicant identified adherence to CGMPs (b) (4). The applicant referred to studies conducted (b) (4) in which the microbial growth was monitored. The applicant also submitted established hold times (based on reports CIN-FD-R-033 and CIN-FD-R-195) (b) (4). These hold times will be documented in the batch record. The maximum holding time is as follows: (b) (4)

(b) (4) These data were submitted to support the proposed lack of end product testing. The applicant also provided the results from 8 batches of PA32540 and 5 batches of PA8140 tablets that had undetectable TAMC and TYMC counts and no *Escherichia coli* present. All 12 batches were produced at commercial scale and were tested using compendial methods.

(b) (4) conducted method validation studies for USP<61> and <62> test methods to support the microbial evaluation (b) (4). Method B929901 (page 49/196) describes studies done for PA-325 (b) (4). The method verification studies supported the proposed use (b) (4). CIN-FD-R-033 describes studies conducted (b) (4)

(b) (4) No organisms were present at any time points. It is unknown whether the omeprazole is antimicrobial in nature.

CIN-FD-R-195 contained results from bulk hold time studies (b) (4)

The applicant updated the post approval stability protocol and commitment to include microbial limits testing (b) (4)

ADEQUATE

Reviewer Comment – The microbiological quality of the drug product is controlled with adequate GMP procedures and established hold times (b) (4). Microbial testing will occur (b) (4)

MEMORANDUM

[Redacted] (b) (4)

END

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/s/

JESSICA COLE
07/08/2013

BRYAN S RILEY
07/08/2013
I concur.

Initial Quality Assessment
Branch 4
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 205-103
Applicant: POZEN, Inc.
Stamp Date: 3/25/2013
Review Date: 5/15/201
PDUFA Date: 1/25/2014
Filing Meeting: 5/08/2013
Proposed Trademark: not yet finalized
Established Name: aspirin and omeprazole
Dosage Form: tablets
Route of Administration: oral
Indication: (b) (4)

CMC Lead: Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	
Comments for 74-Day Letter		<input checked="" type="checkbox"/>

A. Summary

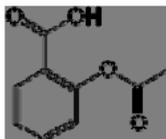
The proposed product is a combination tablet, containing aspirin and omeprazole. It is intended for once daily oral administration (b) (4)

(b) (4) Tablets will be manufactured in two strengths, containing either 325 or 81 mg of delayed release aspirin in the tablet core, with 40 mg of immediate release omeprazole in the film coat.

The product has been developed under IND 78747 and is being filed as a 505(b)(2) application, with Ecotrin® (aspirin, OTC) and Prilosec® (omeprazole, NDA 19810) as the reference listed drugs. Since the product contains two currently approved drugs that have not been previously marketed in combination, this NDA is classified as a type 4 application under the Chemical Classification Code, MAPP 7500.3.

Drug Substances

Aspirin



will be purchased (b) (4)
(b) (4) DMF (b) (4) is referenced for all CMC information regarding the manufacture of aspirin (b) (4) that is used in the drug product.

(b) (4)

Complete CMC information regarding the manufacture and characterization of omeprazole is referred to (b) (4) DMF (b) (4)

Drug Product

PA32540 Tablets (325 mg aspirin/40 mg omeprazole) and PA8140 Tablets (81 mg aspirin/40 mg omeprazole) are oval, blue-green, film coated tablets with "325/40" or "81/40" printed in black on one side. Manufacture will be at (b) (4)

The tablets for both strengths consist of an aspirin core that is coated with (b) (4) film coat (b) (4) as shown below



(b) (4)

The tablet composition is further described as

Components	PA32540 Tablet (mg per unit)	PA8140 Tablet (mg per unit)	Function	Standard (b) (4)
Aspirin (b) (4)	(b) (4)	(b) (4)	(b) (4) Active Ingredient (b) (4)	DMF
Cellulose Microcrystalline (b) (4)	(b) (4)	(b) (4)	(b) (4)	NF
Starch (b) (4)	(b) (4)	(b) (4)	(b) (4)	NF
Silicon Dioxide Colloidal (b) (4)	(b) (4)	(b) (4)	(b) (4)	NF
Stearic Acid (b) (4)	(b) (4)	(b) (4)	(b) (4)	NF (b) (4)
Triethyl Citrate (b) (4)	(b) (4)	(b) (4)	(b) (4)	NF (b) (4)
Omeprazole	40	40	Active Ingredient (b) (4)	USP
Polysorbate 80	(b) (4)	(b) (4)	(b) (4)	NF

Components	PA32540 Tablet (mg per unit)	PA8140 Tablet (mg per unit)	Function	Standard
Sodium Phosphate Dibasic Anhydrous	(b) (4)	(b) (4)	(b) (4)	USP
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Carnauba Wax	(b) (4)	(b) (4)	(b) (4)	NF
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

All excipients are compendial (b) (4) for which DMF references are provided.

(b) (4)

For the 325 mg tablet, the (b) (4)

commercial batch was manufactured (b) (4)

Therefore the 24 months of submitted long term stability data can validly be used in expiration dating the product..

For the 81 mg tablet, (b) (4)

changes between the clinical and commercial formulation will be evaluated by the Biopharmaceutics reviewer. According to the submission, the commercial formulation is identical to the primary stability formulation. However, only 3-months of primary stability data (three batches) have been submitted. Supporting stability data are also provided, but these are for developmental formulations. The company was contacted prior to the filing meeting regarding this deficiency, with the conclusion that a total of 8.5 months of stability data would be submitted by August 3rd (three weeks prior to the midcycle for this NDA), and an additional 11.5 months of stability data would be submitted by November 4th.

The product is packaged in white high density polyethylene (HDPE) with a (b) (4) screwcap closure (b) (4) and stability studies were conducted in this same packaging. For each strength, (b) (4) four packaging configurations has been used in the stability program. FDA agreed to the bracketing approach for the 325 mg tablet prior to NDA submission. (Stability data for all four packaging configurations will be submitted for the 81 mg strength at 8.5 and 11.5 months.)

The drug product specification includes identification tests for both aspirin and omeprazole, HPLC assay for the actives, dosage uniformity (per USP), testing for aspirin and omeprazole related substances, dissolution testing (acid resistance, aspirin dissolution, omeprazole dissolution).

For omeprazole related substances, the limit for individual impurities is (b) (4)%, in conformance with ICH recommendations. For aspirin-related impurities, individual impurity limits are set at (b) (4)%, again in line with ICH recommendations. However, the limit (b) (4) is set at (b) (4)%; the USP limits (b) (4) are set at (b) (4)% for aspirin, (b) (4)% (b) (4) and a (b) (4)% for extended release tablets. The appropriate limit for this product will need to be determined in conjunction with the toxicology reviewer.

Executed batch records are provided for both tablet strengths.

The firm claims categorical exclusion from an environmental assessment in accordance with 21 CFR 25.31(a), because approval of this New Drug Application will not increase the use of either active moiety; the product is a combination drug in which the single product substitutes directly for two approved products that would be administered separately.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

Established name: The applicant proposes (*aspirin delayed release/omeprazole immediate release*) tablets as the established name. Based on recommendations from the Labeling and Nomenclature Committee for an analogous combination product, the established name should be (*aspirin and omeprazole*) delayed release tablets

The biopharmaceutics review has been assigned to Banu Zolnik, Ph.D.

The Micro review has been assigned to Jessica Cole, Ph.D.

B. Critical issues for review

The following issues will require closer scrutiny during the course of the full review of this application:

-- An acceptable (b) (4) limit should be determined for the product in conjunction with the toxicology reviewer.

-- The acceptability of the proposed established name will need to be determined

-- (b) (4)

C. Comments for 74-Day Letter -- None

D. Recommendation – From the CMC perspective this application is fileable

Marie Kowblansky, PhD
CMC Lead

5/17/2013
Date

Moo-Jhong Rhee, PhD
Branch Chief

FILING CHECKLIST

NDA Number:	Supplement Number and Type:	Established/Proper Name:
205-103	original	(aspirin and omeprazole)delayed release tablets
Applicant:	Letter Date:	Stamp Date:
Pozen.		3/25/2013

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

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

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

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		categoryical exclusion

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

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categoryical exclusion been provided?	√		categoryical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	√		referenced to DMF
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		referenced to DMF
14.	Does the section contain information regarding the characterization of the DS?	√		referenced to DMF
15.	Does the section contain controls for the DS?	√		referenced to DMF
16.	Has stability data and analysis been provided for the drug substance?	√		referenced to DMF
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		Executed batch record for each strength
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	√		Not required, methods are located in the body of this electronic submission

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Not required

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		DMFs are referenced for aspirin, omeprazole, coatings, packaging components,

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			No issues for inclusion in the 74-day letter

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
 CMC Lead, Branch IV
 Division of Pre-Marketing Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo Jhong Rhee, Ph.D.
 Branch Chief, Branch IV
 Division of Pre-Marketing Assessment II
 Office of New Drug Quality Assessment

Date

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/s/

MARIE KOWBLANSKY
05/21/2013

MOO JHONG RHEE
05/21/2013
Chief, Branch IV



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

DATE: 16 May 2013

TO: Stacy Barley/Anissa Davis
Regulatory Health Project Manager
CDER/OND/DGIEP

FROM: Jessica G. Cole, PhD
Review Microbiologist
CDER/OPS/New Drug Microbiology Staff
(301) 796-5148

THROUGH: Bryan Riley, PhD
Microbiology Team Leader
CDER/OPS/New Drug Microbiology Staff

SUBJECT: NDA: 205-103
Submission Date: 25 March 2013
Drug Product: PA8140 and PA32540 (aspirin and omeprazole)
Applicant: Pozen, Inc.

A product quality microbiology review of NDA 205-103 is in progress and more information is needed. Please forward the following comment to the applicant.

Microbiology Comment:

You propose to waive microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
 - a. Address how the (b) (4) are controlled for microbial growth (b) (4)
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

MEMORANDUM

3. Describe activities taken when microbiological acceptance criteria are not met at control points.
4. Provide an updated stability schedule to reflect microbial limits testing (b) (4)
 (b) (4)

END

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/s/

JESSICA COLE
05/20/2013

BRYAN S RILEY
05/20/2013
I concur.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	NDA 205-103
Submission Date	3/25/2013
Product name, generic name of the active	PA8140 and PA32540 (aspirin/omeprazole) Tablets
Dosage form and strength	Tablets, 81 mg aspirin/ 40 mg omeprazole and 325 mg aspirin/ 40 mg omeprazole
Applicant	Pozen
Clinical Division	Division of Gastroenterology and Inborn Errors Products
Type of Submission	505 (b) (2)
Biopharmaceutics Reviewer	Banu S. Zolnik, Ph.D.
Biopharmaceutics Team Leader (acting)	Sandra Suarez Sharp, Ph.D.
Acting Supervisor	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	X		Dissolution Method for Aspirin: Acid Resistance Stage: USP I (basket), 100 rpm, 900 mL, 0.1 N HCl Buffer Stage: USP I (basket), 100 rpm, 900 mL, pH 6.8 Phosphate Buffer Dissolution Method for Omeprazole: USP I (basket), 100 rpm, 900 mL, 0.05 M Phosphate Buffer (pH 7.4)
2.	Is the dissolution test part of the DP specifications?	X		Aspirin: <div style="background-color: #cccccc; height: 40px; width: 100%;"></div> (b) (4) Omeprazole: <div style="background-color: #cccccc; height: 40px; width: 100%;"></div> (b) (4)
3.	Does the application contain the dissolution method development report?		X	Data supporting the discriminating capability of the dissolution method are not provided.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

4.	Is there a validation package for the analytical method and dissolution methodology?	X		HPLC method for Aspirin and Omeprazole: (b) (4)
5.	Does the application contain in vitro alcohol induced dose dumping studies?		X	In vitro alcohol induced dose dumping studies were not provided as per requested during IND 78,747 Type A Meeting dated 9/21/2012 minutes.
6.	Does the application include a biowaiver request?		X	
7.	Is there information provided to support the lower strength (s)?		X	For PA 8140 strength a 3-way cross-over study (PA8140-102) submitted to assess bioequivalence of PA8140 Tablets to the RLD based on pharmacokinetics of acetylsalicylic acid. OCP will review the BE studies. For PA8140 strength an open label, single blind, randomized three arm, parallel group study to evaluate the effects on the gastroduodenal mucosa of PA8140 Administered with and without Celecoxib (200 mg) and Enteric Coated (EC) Aspirin 81 mg when administered with Celecoxib, Study PA08140-101 was submitted. The study will be reviewed by the Clinical Team.
8.	Does the application include an IVIVC model?		X	
9.	Is information such as BCS classification mentioned, and supportive data provided?		X	
10.	Is information on mixing the product with foods or liquids included?		X	Not applicable.
11.	Is there any in vivo BA or BE information in the submission?	X		Several BE and Clinical Studies (see summary PK/PD and Clinical Studies Tables below for PA 8140 and PA32540) are included in the present submission and will be reviewed by OCP and Clinical teams.
12.	Are there any manufacturing changes implemented to the clinical trial and bio batch formulations?	X		See Tables 2 and 3 below.
13.	Is there any data submitted to support the manufacturing changes	X		Comparative dissolution studies were submitted for Bio, commercial and stability batches in which formulations differed from each other. Refer to Table 2 and 3 below.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

14.	Is there any data submitted to support the proposed dissolution specification?	X		Dissolution studies were submitted for the Bio, commercial and stability batches.
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B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
15.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
16.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
17.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
18.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		Comments will be sent to the Applicant as part of the 74-day letter. The comments are outlined under the Recommendation Section of this filing review.
19.	Comment to the Clinical and Clinical Pharmacology review teams			PA8140 and PA32540 (b) (4) <div style="background-color: #cccccc; width: 100%; height: 20px; margin: 5px 0;"></div> BE data and/or clinical efficacy and safety information are needed to support the lower strength. In addition, there are major changes between the Phase 1 and to-be-marketed formulation for PA8140; furthermore, the PK and/or PD for the omeprazole component were not evaluated with the to-be-marketed formulation. Therefore, we recommend that the acceptability of this lower strength to be determined by the Clinical Pharmacology and Clinical Review teams.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY

The Applicant, Pozen submitted 505(b)(2) NDA application for PA8140 and PA 32540 tablets which contain omeprazole and aspirin for use in the secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin associated gastric ulcers. Both PA32540 and PA8140 Tablets consist of an aspirin core with delayed release dependent on pH ^{(b) (4)} and omeprazole coat with immediate release characteristics. Omeprazole degrades rapidly in the gastric media.

PA8140 formulation contains 81 mg Aspirin, and 40 mg omeprazole. PA32540 mg formulation contains 325 mg Aspirin and 40 mg omeprazole.

For PA8140 strength, the Applicant developed two different formulations (Phase 1 Formulation and To-Be-Marketed (Primary Stability) of PA08140 strength. There are major differences ^{(b) (4)} between these two formulations (Table 2 below). The Applicant conducted PA08140-101 study (PD study for omeprazole component) to evaluate the effects of PA08140 on the gastroduodenal mucosa with Phase 1 Formulation, and PA8140-102 BA/PK study to assess the bioavailability of acetylsalicylic acid with the To-Be-Marketed Formulations. Therefore, the acceptability of the lower strength is a review issue and will be determined by the clinical pharmacology and clinical teams..

For PA32540 strength, The Applicant developed Initial Phase 1, Phase 1 and Phase3/BE and To-Be-Marketed formulations. There are major formulation differences between Initial Phase 1 and Phase 1 formulation. However, most of the clinical safety and efficacy studies are conducted on the Phase 3/BE formulation, and there are minor formulation changes between the Phase 3/BE formulation and To-Be-Marketed Formulation. Comparative Dissolution Data is provided to support the formulation changes between the phase 3 and commercial formulations. PA32540-115 Study is submitted to support the bioequivalence of PA32540 to the RLD using acetylsalicylic acid as the analyte.

Figure 1 shown below is the schematic of the product.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Figure 1: Schematic of PA32540 and PA8140 Tablet (not to scale)



Table 1: Comparison of proportionality for PA32540 and PA8140 Tablets

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Reviewer's comment: PA8140 and PA32540

(b) (4)

BE data and/or clinical efficacy and safety information are needed to support the lower strength.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Table 2: Composition Information for Aspirin/Omeprazole, 81 mg/40 mg for Phase 1 and Primary Stability Formulations

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill. The redaction covers the entire content of Table 2.

Reviewer's comment: There are major compositional differences between the Phase 1 (BE study for aspirin) and Primary Stability batch for PA 8140. Figures below show comparative dissolution profiles of Primary Stability Batch and BE batch for Aspirin and Omeprazole.

Figure 12 PA8140 Tablet Aspirin Dissolution – Primary Stability Batches



Figure 13 PA8140 Tablet Omeprazole Dissolution – Primary Stability Batches



PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Table 3: Composition Information for Aspirin/Omeprazole, 325 mg/40 mg for Initial Phase 1, Phase 1, and Phase3/BE and Primary Stability Studies

(b) (4)



Reviewer's comment: There are formulation changes made to the primary stability batches as compared to the Phase 3 and BE batches. (b) (4)

These changes are considered minor by the ONDQA review team.

Below is the comparative dissolution profiles of Primary Stability, BE and Phase 3 Clinical Study Batches for Aspirin and Omeprazole Dissolution.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Figure 16 PA32540 Tablet Aspirin Dissolution – Primary Stability, Bioequivalence, and Phase 3 Clinical Study Batches



Figure 17 PA32540 Tablet Omeprazole Dissolution – Primary Stability, Bioequivalence, and Phase 3 Clinical Study Batches



Reviewer’s comment: The Applicant did not provide comparative dissolution profile of the batch 3078656R to the other clinical batches, and this comment will be conveyed to the Applicant in the 74-day letter.

Proposed Dissolution Method and Acceptance Criteria:

Proposed Dissolution Method Aspirin						Acceptance Criteria (% of the labeled amount dissolved)
Stage	USP Apparatus	Rotation Speed	Medium Volume	Temp	Medium	
Acid Resistance Stage *	USP I (basket)	100 rpm	900 mL	37°C ±0.5°C	0.1 N HCl	81/40 mg: NMT (b) (4) %
						325/40 mg: NMT (b) (4) %
Buffer Stage	USP I (basket)	100 rpm	900 mL	37°C ±0.5°C	pH 6.8 Phosphate Buffer	81/40 mg: (b) (4) % in (b) (4) minutes
						325/40 mg: Q= (b) (4) % at (b) (4) minutes

(b) (4)

Proposed Dissolution Method Omeprazole					Acceptance Criteria (% of the labeled amount dissolved)
USP Apparatus	Rotation Speed	Medium Volume	Temp	Medium	
USP I (basket)	100 rpm	900 mL	37°C ±0.5°C	0.05 M Phosphate Buffer (pH 7.4)**	81/40 mg: Q= (b) (4) % at (b) (4) minutes 325/40 mg: Q= (b) (4) % at 45 minutes

**

(b) (4)

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

(b) (4)

PA 8140 Tablets Dissolution Profile

PA 32540 Tablets Dissolution Profile

Figure 3 Typical Aspirin and Omeprazole Dissolution Profiles for PA8140 Tablets (b) (4)



Figure 2 Typical Aspirin and Omeprazole Dissolution Profiles for PA32540 Tablets (b) (4)



The applicant provided the following dissolution data in the submission:

- 1) For PA 32540 strength, Aspirin and Omeprazole dissolution were evaluated in the following dissolution method conditions: 0.1 N HCl, pH (b) (4) 7.4 media.
- 2) For PA 32540 strength, Aspirin and Omeprazole dissolution were evaluated in at pH 7.4 media using USP Apparatus I (baskets) at (b) (4) 100 rpm (b) (4)
- 3) For PA 8140 strength, Aspirin and Omeprazole dissolution were evaluated in the following dissolution method conditions: pH 6.8 and 7.4 (b) (4)

PK/PD and Clinical Studies Summary Table for PA 8140

Study ID	Objective	Primary End point	Design	Test Article	Lot Number	Manufacturer	Formulation	Dissolution Information for ASPIRIN	Dissolution Information For OMEPRAZOLE	Stability Batch
PA08140-102	BA and PK	plasma level of acetylsalicylic acid	OL, R, Reference Replicated, 3 way crossover	PA 8140 and EC Aspirin 81 mg	3101868R	(b) (4)	Primary stability PA8140	YES	YES	YES
					3101869R			YES	YES	YES
					3101870R			YES	YES	YES
Study ID	Objective	Primary Endpoint	Design	Test Article	Lot Number	Manufacturer	Formulation	Dissolution Information	Dissolution Information	Stability Batch
PA 08140-101	Gastroduodena l Mucosal damage	Proportion grade 3/4 Lanza Score	R, PG, AC, single blind (investigator)	PA8140 PA8140 +celecoxib EC-aspirin 81 mg Celecoxib	L0200002	(b) (4)	Phase 1 for 8140 Tablets	NO	NO	NO

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

PK/PD and Clinical Studies Summary Tables for PA 32540

325 mg Strength	Study ID	Objective	Primary Endpoint	Design	Test Article	Lot Number	Manufacturer	Formulation	Dissolution Information for ASPIRIN	Dissolution Information For OMEPRAZOLE	Stability Batch
325 mg Strength	PA32540-104	BA and PK	plasma level of salicylic acid	OL, R, 3 way crossover	PA32540	3061488R	(b) (4)	Table 4: Phase 3/BE	YES	YES	NO
					aspirin component of PA32540	3063651R (for aspirin component of PA32540)		NA			
	PA32540-105	Food effect	Plasma levels of salicylic acid and omeprazole	OL, R, 3way crossover, food effect (5 minutes after high fat, and 60 min after high fat, and then overnight fast)	PA32540	3079494R	(b) (4)	Table 4: Phase 3/BE	YES	YES	NO
	PA32540-113	PK and relative BA	Plasma levels of salicylic acid and omeprazole	OL, R, AC, 4 way crossover	PA 32540 EC aspirin 325 mg/EC omeprazole	3079494R Ecotrin batch 12081 and Prilosec		GSK, AstraZeneca	Table 4: Phase 3 and BE NA	YES NA	YES NA
					EC aspirin 325 mg alone	Ecotrin	GSK	NA			
					EC omeprazole 40 mg alone	Prilosec	AstraZeneca	NA			
	PA32540-115	BA and PK	Plasma levels of acetylsalicylic acid	OL, R, reference replicated 3 way crossover	PA 32540	3076610R	(b) (4)	Table 4: Phase 3 and BE	YES	YES	NO
					EC aspirin 325 mg	Ecotrin batch 12777	GSK	NA			
					EC aspirin 325 mg	Ecotrin	GSK	NA			

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Other clinical										
PA325-101	Gastroduodenal Mucosal damage also PK	Proportion grade 3/4 Lanza Score	R, PG, AC, single blind (investigator)	PA32520	KK2005011	(b) (4)	Table 4: Initial Phase 1	NO	NO	
				EC-aspirin 325 mg			NA			
PA325-102	Gastroduodenal Mucosal damage	Proportion grade 3/4 Lanza Score	R, PG, AC, single blind (investigator)	PA32520	KK2005011	(b) (4)	Table 4: Initial Phase 1	NO	NO	
				EC-aspirin 81 mg			NA			
PA325-106	Gastroduodenal Mucosal damage	Proportion grade 3/4 Lanza Score	R, PG, AC, single blind (investigator)	PA32540	L0106008	(b) (4)	Table 4: Phase 1	YES (compared to 3061488R, 3073022R, 3076610R)	YES (compared to 3061488R, 3073022R, 3076610R)	
				EC-aspirin 325 mg			NA			
PA32540-109	Gastroduodenal Mucosal damage	Proportion grade 3/4 Lanza Score	R, PG, AC, single blind (investigator)	PA32540	3061488R	(b) (4)	Table 4: Phase 3 and BE	YES	YES	
				PA32540+celecoxib			NA			
PA32540-110	Inhibition of platelet aggregation	%IPS using chronolog ADP agonist	OL, R, AC, crossover	Clopidogrel/EC 325 mg aspirin QD	3061488R	(b) (4)	NA			
				PA32540 in the morning/clopidogrel (10 hours apart)			Table 4: Phase 3 and BE	YES	YES	
PA32540-111	Inhibition of platelet aggregation	%IPS using chronolog ADP agonist	OL, R, AC, crossover	PA32540 in the morning/clopidogrel (10 hours apart)	3079494R	(b) (4)	Table 4: Phase 3 and BE	YES	YES	
				EC-aspirin 81 mg QD +EC omeprazole 40			NA			
PA32540-112	PD effect on intragastric PH and PK	Intragastric PH percent time>4 /PK end point omeprazole and salicylic acid	OL, R, AC, 2 way crossover	PA32540	3079494R	(b) (4)	Table 4: Phase 3 and BE	YES	YES	
				EC omeprazole 40 mg/ EC aspirin 325 mg			NA			
PA32540-301	Reduction risk of Gastric Ulcers	Cumulative incidence of subjects with gastric ulcers by endoscopy throughout 6months of treatment	R, DB, PG, AC (DB: double blind)	PA32540	3073022R and 3076610R and 3079494R	(b) (4)	Table 4: Phase 3 and BE	YES	YES	
				EC aspirin 325 mg			Placebo	YES (for aspirin)	NA	
PA32540-302	Reduction risk of Gastric Ulcers	Cumulative incidence of subjects with gastric ulcers by endoscopy throughout 6months of treatment	R, DB, PG, AC (DB: double blind)	PA32540	3073022R and 3076610R and 3079494R	(b) (4)	Table 4: Phase 3 and BE	YES	YES	
				EC aspirin 325 mg			Placebo	YES (for aspirin)	NA	
PA32540-303	Long term safety of PA32540 in at risk patients	Adverse events	OL	PA32540	3073022R and 3076610R and 3078656R (drug substance omeprazole manufactured by different company)	(b) (4)	Table 4: Phase 3 and BE BUT check 3078656R Stability or not	NO for 3078656R others yes	NO for 3078656R others yes	
STABILITY BATCH					3077420R and 3077422R and 3077423R	(b) (4)		YES	YES	Stability Batch

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

The Biopharmaceutics review will be focused on **1)** the evaluation and acceptability of the proposed dissolution methods and acceptance criteria.

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 205103 Aspirin Omeprazole Tablets is fileable. The following comments should be conveyed to the Applicant in the 74-Day Letter.

- 1) *Solubility data for the drug substance covering the physiological pH range.*
- 2) *Provide data supporting the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.*
- 3) *Provide comparative dissolution profile of the batch 3078656R to the other clinical batches.*
- 4) *You have not provided In Vitro Alcohol Induced Dose Dumping Studies for both strengths as per recommended during IND 78,747 Type A Meeting minutes dated 9/21/2012. We are concerned that your delayed release (DR) product may release its entire contents (“dose dumping”) in the stomach when co-administered with alcohol defeating the purpose of the formulation. Therefore evaluate the potential for a drug-alcohol interaction with your DR product in in vitro settings.*
 - *Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed in 0.1 N HCl and in the proposed QC medium. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.*
 - *The following alcohol concentrations for the in vitro dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.*
 - *The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.*
 - *The f₂ values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).*

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

{See appended electronic signature page}

Banu S. Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

05/14/13
Date

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Team leader (acting)
Office of New Drug Quality Assessment

05/14/13
Date

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/s/

BANU S ZOLNIK
05/15/2013

SANDRA SUAREZ
05/15/2013

**ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 205103/000
App Date: 25-MAR-2013
Regulatory: 25-JAN-2014

Action Goal:
District Goal: 26-NOV-2013

Applicant: POZEN INC
1414 RALEIGH RD STE 400
CHAPEL HILL, NC 275178834

Brand Name: PA8140 and PA32540 (two strengths of a f
Estab. Name:
Generic Name: PA8140 and PA32540 (two strengths of a f

Priority:
App Code: 180

Product Number; Dosage Form; Ingredient; Strengths
001; TABLET; ASPIRIN; 81MG
001; TABLET; OMEPRAZOLE; 40MG
002; TABLET; ASPIRIN; 325MG
002; TABLET; OMEPRAZOLE; 40MG

Application Comment:

App Contacts:	Z. GE	Prod Qual Reviewer	3017961358
	C. TRAN-ZWANETZ	Product Quality PM (HFD-800)	3017963877
	S. BARLEY	Regulatory Project Mgr	3017962137
	M. KOWBLANSKY	Team Leader	3017961390

Overall Recommendation: PENDING on 02-MAY-2013 by EES_PROD
PENDING on 02-MAY-2013 by EES_PROD

**ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

- Responsibilities:
- DRUG SUBSTANCE OTHER TESTER
 - FINISHED DOSAGE MANUFACTURER
 - FINISHED DOSAGE OTHER TESTER
 - FINISHED DOSAGE PACKAGER
 - FINISHED DOSAGE STABILITY TESTER

Establishment Description: PROVIDES FOR MANUFACTURING, BULK PACKAGING, PACKAGING, STABILITY TESTING, AND QUALITY CONTROL TESTING OF DP. ALSO DS TESTING. (on 02-MAY-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)
 File: TABLETS, PROMPT RELEASE OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u> 3MITTED TO OC	02-MAY-2013			<u>Reason</u>	TRANZWANETZC
3MITTED TO DO	02-MAY-2013	10-Day Letter			WILLIAMSJU

**ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

F AADA:

- Responsibilities:
- DRUG SUBSTANCE LABELER
 - DRUG SUBSTANCE MANUFACTURER
 - DRUG SUBSTANCE OTHER TESTER
 - DRUG SUBSTANCE PACKAGER

Establishment: PROVIDES FOR SITE FOR MANUFACTURING, QUALITY CONTROL TESTING, PACKAGING, LABELLING FOR
 Comment: OMEPRAZOLE, USP (on 16-APR-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)
 File: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
3MITTED TO OC	02-MAY-2013				TRANZWANETZC
RECOMMENDATION	02-MAY-2013			ACCEPTABLE BASED ON PROFILE	WILLIAMSJU

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)
[REDACTED] (b) (4)
File: **AADA:**

- Responsibilities:**
- DRUG SUBSTANCE LABELER
 - DRUG SUBSTANCE MANUFACTURER
 - DRUG SUBSTANCE OTHER TESTER
 - DRUG SUBSTANCE PACKAGER

Establishment Name: PROVIDES FOR MANUFACTURING, QUALITY CONTROL TESTING, PACKAGING, AND LABELLING FACILITY FOR ASPIRIN,
File: (b) (4) NF DRUG SUBSTANCE. (on 16-APR-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)
[REDACTED] (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
COMMITTED TO OC	02-MAY-2013				TRANZWANETZC
RECOMMENDATION	02-MAY-2013			ACCEPTABLE BASED ON PROFILE	WILLIAMSJU

**ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

F AADA:

- Responsibilities:
- DRUG SUBSTANCE LABELER
 - DRUG SUBSTANCE MANUFACTURER
 - DRUG SUBSTANCE OTHER TESTER
 - DRUG SUBSTANCE PACKAGER

Establishment Name: PROVIDES FOR SITE FOR MANUFACTURING, QUALITY CONTROL TESTING, PACKAGING, LABELLING FOR OMEPRAZOLE, USP (on 16-APR-2013 by C. TRAN-ZWANETZ (HFD-800) 3017963877)
 File: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
COMMITTED TO OC	02-MAY-2013				TRANZWANETZC
RECOMMENDATION	02-MAY-2013			ACCEPTABLE BASED ON PROFILE	WILLIAMSJU