CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205103Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205103 SUPPL # HFD # 180

Trade Name Yosprala delayed-released Tablets

Generic Name aspirin 81 mg/omeprazole 40 mg, and aspirin 325 mg/omeprazole 40 mg

Applicant Name Aralez Pharmaceuticals R&D Inc.

Approval Date, If Known 09/14/2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

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

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☒ NO ☐

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

No

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☒ NO ☐

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

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not

essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Study 1: PA32540-301
Study 2: PA32540-302

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

Not applicable

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

Study 1: PA32540-301

Study 2: PA32540-302

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

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

Investigation #1: PA32540-301 !

IND # 78,747 YES ☒ ! NO ☐
! Explain:

Investigation #2: PA32540-302 !

IND # 78,747 YES ☒ ! NO ☐
! Explain:

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

Investigation #1 !

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !

YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that

the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: CAPT Mimi T. Phan
Title: Regulatory Project Manager
Date: 09/12/2016

Name of Division Director signing form: Donna Griebel
Title: Division Director

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

Attachment for Part II Question #2

NDA#	BRAND NAME	GENERIC NAME	DOSAGE FORM
N007337	PERCODAN	ASPIRIN; OXYCODONE HYDROCHLORIDE	TABLET
N007337	PERCODAN	ASPIRIN; OXYCODONE HYDROCHLORIDE; OXYCODONE TEREPHTHALATE	TABLET
N007337	PERCODAN-DEMI	ASPIRIN; OXYCODONE HYDROCHLORIDE; OXYCODONE TEREPHTHALATE	TABLET
N010996	DARVON COMPOUND	ASPIRIN; CAFFEINE; PROPOXYPHENE HYDROCHLORIDE	CAPSULE
N010996	DARVON COMPOUND-65	ASPIRIN; CAFFEINE; PROPOXYPHENE HYDROCHLORIDE	CAPSULE
N010996	DARVON W/ ASA	ASPIRIN; PROPOXYPHENE HYDROCHLORIDE	CAPSULE
N011483	SYNALGOS-DC	ASPIRIN; CAFFEINE; DIHYDROCODEINE BITARTRATE	CAPSULE
N011702	EQUAGESIC	ASPIRIN; MEPROBAMATE	TABLET
N012281	ROBAXISAL	ASPIRIN; METHOCARBAMOL	TABLET
N012365	SOMA COMPOUND	ASPIRIN; CARISOPRODOL	TABLET
N012366	SOMA COMPOUND W/ CODEINE	ASPIRIN; CARISOPRODOL; CODEINE PHOSPHATE	TABLET
N013416	NORGESIC	ASPIRIN; CAFFEINE; ORPHENADRINE CITRATE	TABLET
N013416	NORGESIC FORTE	ASPIRIN; CAFFEINE; ORPHENADRINE CITRATE	TABLET
N016030	8-HOUR BAYER	ASPIRIN	TABLET, EXTENDED RELEASE
N016030	MEASURIN	ASPIRIN	TABLET, EXTENDED RELEASE
N016829	DARVON-N W/ ASA	ASPIRIN; PROPOXYPHENE	CAPSULE

		NAPSYLATE	
N016863	DARVON-N W/ ASA	ASPIRIN; PROPOXYPHENE NAPSYLATE	TABLET
N016891	TALWIN COMPOUND	ASPIRIN; PENTAZOCINE HYDROCHLORIDE	TABLET
N017534	FIORINAL	ASPIRIN; BUTALBITAL; CAFFEINE	CAPSULE
N017534	FIORINAL	ASPIRIN; BUTALBITAL; CAFFEINE	TABLET
N019429	FIORINAL W/CODEINE	ASPIRIN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE	CAPSULE
N020802	EXCEDRIN (MIGRAINE)	ACETAMINOPHEN; ASPIRIN; CAFFEINE	TABLET
N020884	AGGRENOX	ASPIRIN; DIPYRIDAMOLE	CAPSULE, EXTENDED RELEASE
N021317	BAYER EXTRA STRENGTH ASPIRIN FOR MIGRAINE PAIN	ASPIRIN	TABLET
N021387	PRAVIGARD PAC (COPACKAGED)	ASPIRIN; PRAVASTATIN SODIUM	TABLET, TABLET
N021387	PRAVIGARD PAC (COPACKAGED)	ASPIRIN; PRAVASTATIN SODIUM	TABLET, TABLET
N021387	PRAVIGARD PAC (COPACKAGED)	ASPIRIN; PRAVASTATIN SODIUM	TABLET, TABLET
N021387	PRAVIGARD PAC (COPACKAGED)	ASPIRIN; PRAVASTATIN SODIUM	TABLET, TABLET
N021387	PRAVIGARD PAC (COPACKAGED)	ASPIRIN; PRAVASTATIN SODIUM	TABLET, TABLET
N021387	PRAVIGARD PAC (COPACKAGED)	ASPIRIN; PRAVASTATIN SODIUM	TABLET, TABLET
N200671	DURLAZA	ASPIRIN	CAPSULE, EXTENDED RELEASE
N203697	ASPIRIN	ASPIRIN	CAPSULE

N019810	PRILOSEC	OMEPRAZOLE	CAPSULE, DELAYED REL PELLETS
N019810	PRILOSEC	OMEPRAZOLE	CAPSULE, DELAYED REL PELLETS
N019810	PRILOSEC	OMEPRAZOLE	CAPSULE, DELAYED REL PELLETS
N021229	PRILOSEC OTC	OMEPRAZOLE MAGNESIUM	TABLET, DELAYED RELEASE
N021636	ZEGERID	OMEPRAZOLE; SODIUM BICARBONATE	FOR SUSPENSION
N021636	ZEGERID	OMEPRAZOLE; SODIUM BICARBONATE	FOR SUSPENSION
N021849	ZEGERID	OMEPRAZOLE; SODIUM BICARBONATE	CAPSULE
N021849	ZEGERID	OMEPRAZOLE; SODIUM BICARBONATE	CAPSULE
N021850	ZEGERID	MAGNESIUM HYDROXIDE; OMEPRAZOLE; SODIUM BICARBONATE	TABLET, CHEWABLE
N021850	ZEGERID	MAGNESIUM HYDROXIDE; OMEPRAZOLE; SODIUM BICARBONATE	TABLET, CHEWABLE
N022032	OMEPRAZOLE	OMEPRAZOLE	TABLET, DELAYED RELEASE
N022056	PRILOSEC	OMEPRAZOLE MAGNESIUM	FOR SUSPENSION, DELAYED RELEASE
N022056	PRILOSEC	OMEPRAZOLE MAGNESIUM	FOR SUSPENSION, DELAYED RELEASE
N022281	ZEGERID OTC	OMEPRAZOLE; SODIUM BICARBONATE	CAPSULE
N022283	ZEGERID OTC	OMEPRAZOLE; SODIUM BICARBONATE	FOR SUSPENSION
N022456	MAGNESIUM HYDROXIDE AND	MAGNESIUM HYDROXIDE; OMEPRAZOLE; SODIUM	TABLET

	OMEPRAZOLE AND SODIUM BICARBONATE	BICARBONATE	
N022456	MAGNESIUM HYDROXIDE AND OMEPRAZOLE AND SODIUM BICARBONATE	MAGNESIUM HYDROXIDE; OMEPRAZOLE; SODIUM BICARBONATE	TABLET
N050824	OMEPRAZOLE AND CLARITHROMYCIN AND AMOXICILLIN	AMOXICILLIN; CLARITHROMYCIN; OMEPRAZOLE	CAPSULE,TABLET, CAPSULE, DELAYED RELEASE

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

/s/

MIMI T PHAN
09/14/2016

DONNA J GRIEBEL
09/14/2016

EXCLUSIVITY SUMMARY

NDA # 205103 SUPPL # N/A HFD # 180

Trade Name Yosprala

Generic Name aspirin/omeprazole

Applicant Name Pozen, Inc.

Approval Date, If Known April 25, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Three years

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

YES ☐ NO ☒

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

No

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA#	019810, 022056 OTC: 021229	Omeprazole (Prilosec)
NDA#	n/a	EC Aspirin 81mg, 325mg
NDA#		

2. Combination product.

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

YES ☒ NO ☐

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

NDA#	019810, 022056 OTC: 021229	Omeprazole Prilosec
NDA#		
NDA#	n/a	EC ASA 81mg, 325mg

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or

sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

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

The approval was based on the results of the clinical trials that were submitted in the application 1) Study PA32540-301 and 2) Study PA32540-302

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

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

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

Investigation #1Study PA32540-301 YES ☐ NO ☒

Investigation #2 Study PA32540-302 YES ☐ NO ☒

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

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

Investigation #1 Study PA32540-301 YES ☐ NO ☒

Investigation #2 Study PA32540-302 YES ☐ NO ☒

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

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

Study PA32540-301 and Study PA32540-302

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

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

Investigation #1

IND # 78747 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # 78747 YES ☒ ! NO ☐
! Explain:

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

N/A

Investigation #1

YES ☐
Explain:

NO ☐
Explain:

Investigation #2

YES ☐
Explain:

NO ☐
Explain:

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

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Stacy Barley
Title: Senior Regulatory Project Manager
Date:

Name of Office/Division Director signing form: Donna Griebel
Title: Director

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

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Phone: 919.913.1030 | Fax: 919.913.1039
www.pozen.com

NDA # 205103

PA8140 and PA32540 (aspirin 81 mg or 325 mg/omeprazole 40 mg) Tablets

MODULE 1.3.3

DEBARMENT CERTIFICATION

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

SIGNED: Paul A. Ossi DATE Jan. 31, 2013

TITLE: SR VICE PRESIDENT, REGULATORY

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205103 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Yosprala Established/Proper Name: aspirin 81 mg/omeprazole 40 mg; aspirin 325 mg/omeprazole 40 mg Dosage Form: delayed-release tablets		Applicant: Aralez Pharmaceuticals Trading DAC Agent for Applicant (if applicable): Aralez Pharmaceuticals R&D Inc.
RPM: CAPT Mimi T. Phan		Division: Division of Gastroenterology and Inborn Errors Products

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

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 07/15/2016

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

❖ Actions	
• Proposed action • User Fee Goal Date is 09/14/2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CRs: 12/16/14, 4/25/2014
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

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

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

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP; 9/14/16 CRs: 12/16/14, 4/25/14
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters: 5/27/16, 9/13/13, 6/21/13 Reviews: 5/27/16, 9/12/13, 6/21/13
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 5/24/13 DMEPA: ☐ None 7/28/16, 10/8/14, 9/29/14, 12/03/13 DMPP/PLT (DRISK): ☐ None 8/11/16, 11/19/14, 4/22/14 OPDP: ☐ None 8/8/16,4/21/14 SEALD: ☒ None 4/24/14 CSS: ☒ None Product Quality ☒ None Other: ☐ None DPMH: 8/29/16, 8/12/16, 12/20/13
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	5/22/2013 ☐ Not a (b)(2) 8/15/16, 3/18/14
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 09/25/2013 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	9/2/16, 8/30/16, 8/25/16, 8/17/16, 8/10/16, 7/13/16, 6/7/16, 5/12/16, 4/26/16, 3/23/16, 3/18/16, 10/27/14, 10/10/14, 7/15/14, 4/22/14, 4/18/14, 4/14/14, 4/11/14,3/29/14, 3/19/14, 1/23/14,12/19/13, 11/7/13, 11/4/13,11/1/13, 10/11/13, 10/4/13,9/18/13, 9/6/13, 7/25/13, 6/24/13,5/31/13, 5/23/13, 5/17/13, 5/5/13,4/12/13, 4/4/13
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	12/3/13, 10/24/13, 10/7/13
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 1/28/15 (type A) 8/21/12 (Type A), 4/23/12 (Pre-NDA), 1/31/12 (Type A), 3/30/11 (Pre-NDA/type C), 10/2/08 (Type A)
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 9/14/16, 4/25/14
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 9/14/16, 04/25/14
PMR/PMC Development Templates *(indicate total number)*	☐ None 9/14/16
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	11/24/14, 4/18/2014, 4/4/14, 3/21/14, 5/13/13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	04/16/2014 (also see page 17 of 03/21/14 clinical review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None PMHS: 12/22/13; DCRP: 1/16/14, 10/21/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested review-12/11/13; letters- 9/11/13, 8/29/13
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 3/28/2014, also signed filing review on 5/21/13
Statistical Review(s) *(indicate date for each review)*	☐ None 7/11/16; 3/28/14; 5/21/2013

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 8/12/16, 11/24/14, 4/18/2014, 5/10/13
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 8/19/16, 8/8/16, 11/14/13
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 8/5/16, 11/21/14, 12/13/2013, 4/29/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 8/18/16, 4/24/14, 11/21/13, 11/14/13, 7/8/13, 5/21/13, 5/15/13
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None ONDQA BioPharm: 03/21/14; microbiology quality:7/8/13, 5/20/13
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	11/21/13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	Date completed:8/8/16 ☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done **N/A**
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

MIMI T PHAN
09/29/2016

From:	Phan, Mimi
To:	Peggy Berry
Cc:	Chung, Mary; Phan, Mimi
Subject:	RE: NDA 205103 Yosprala labeling minor corrections
Date:	Friday, September 02, 2016 11:23:19 AM

Ms. Berry,
There are a couple of minor corrections/edits to the labels. Below are the following corrections/edits to the PI

1) In the table of content on page 2, sub-section 8.3, please remove the word "infertility"
2) On page 19 Section 8.3 heading is the following
   8.3 Females and Males of Reproductive Potential Infertility- "Infertility" should be removed from the heading.

Below is the following edits to the Medguide

1) On page 1, line 3 from the bottom up it reads "YOSPRALA has not been shown to reduce the risk of bleeding in the stomach or intestines that is caused by aspirin"

We added a period [.] after the word aspirin Thus it should now reads "YOSPRALA has not been shown to reduce the risk of bleeding in the stomach or intestines that is caused by aspirin."

Please confirm your receipt of this correspondence and submit your response to the NDA by Wednesday, September 7, 2016. Thank you.

V/R,

mi²

Mimi T. Phan, Pharm.D.
CAPT, U.S. Public Health Service
SR Program Management Officer
FDA/CDER/OND/ODEIII/DGIEP
10903 New Hampshire Ave
WO22, Room 5236
Silver Spring, MD 20993
Office: 301-796-5408

From: Peggy Berry [mailto:pberry@aralez-contractor.com]
Sent: Thursday, September 01, 2016 5:42 PM
To: Phan, Mimi
Cc: Chung, Mary
Subject: Re: Yosprala NDA

We will have it through the gateway early next week.

Peggy

On Sep 1, 2016, at 3:26 PM, Phan, Mimi <Mimi.Phan@fda.hhs.gov> wrote:

Ms. Berry,
Thank you for sending the revised bottle labels. Please ensure to submit this to the NDA as draft proposed container labels. Please note that labeling (i.e., PI, medguide, container labels) should NOT be considered final until it is provided with the action letter on action date.

R,

mi²

Mimi T. Phan, Pharm.D.
CAPT, U.S. Public Health Service
FDA/CDER/OND/ODEIII/DGIEP
Office: 301-796-5408

From: Peggy Berry [mailto:pberry@aralez-contractor.com]
Sent: Thursday, September 01, 2016 3:10 PM
To: Phan, Mimi; Chung, Mary
Subject: Yosprala NDA

Hi Mimi,
Attached are the revised labels.
Peggy

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/s/

MIMI T PHAN
09/02/2016

From:	Phan, Mimi
To:	"Peggy Berry"
Cc:	Chung, Mary; Phan, Mimi
Subject:	RE: NDA 205103 Yosprala Post Marketing Requirements (PMRs)
Date:	Tuesday, August 30, 2016 2:44:00 PM

Greetings Ms. Berry,
This is an acknowledgement to confirm that we have agreed on your proposed timeline. Please submit the agreement to the NDA no later than 9/1/2016. Thank you very much.

R,

mi²

Mimi T. Phan, Pharm.D.
CAPT, U.S. Public Health Service
FDA/CDER/OND/ODEIII/DGIEP
Office: 301-796-5408

From: Peggy Berry [mailto:pberry@aralez-contractor.com]
Sent: Tuesday, August 30, 2016 8:33 AM
To: Phan, Mimi
Cc: Chung, Mary
Subject: RE: NDA 205103 Yosprala Post Marketing Requirements (PMRs)

Hi Mimi,

Here is our response to your email regarding the postmarketing requirements (PMRs) for the Yosprala NDA 205103.

We agree to conduct the PMRs, however we request a minor modification to the proposed timelines. Based on the expertise required, the size of our organization and the available resources required to fulfill this request, we propose the following timelines – essentially 2 months later for all activities.

In Vitro Study:

Final Protocol Submission:	*1/15/2017*
Study/Trial Completion:	*04/01/2017*
Final Report Submission:	*06/01/2017*

Clinical PK Study:

Final Protocol Submission:	*11/01/2017*
Study/Trial Completion:	*03/01/2018*
Final Report Submission:	*06/01/2018*

The clinical PK study timing has been adjusted relative to the revision to the in vitro study. It is also important to note that the outcome of the in vitro study, the ability to appropriately assess degradants in vivo and FDA feedback during the process may impact this proposed timing.

Let me know if you need additional information.

Also, please let me know if this response should be submitted as an official sequence through the Gateway, or if this email is sufficient.

Thanks!
Peggy

From: Phan, Mimi [mailto:Mimi.Phan@fda.hhs.gov]
Sent: Friday, August 26, 2016 7:02 PM
To: Peggy Berry
Cc: Chung, Mary; Phan, Mimi
Subject: NDA 205103 Yosprala Post Marketing Requirements (PMRs)

Dear Ms Berry,
Reference is made to your New Drug Application (NDA) 205103 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole) tablet dated March 14, 2016.

We have the following proposed Post Marketing Requirements (PMR) for this application. Please confirm your agreement with these requirements, including agreement with the proposed milestone dates by Tuesday, August 30, 2016.

Post Marketing Requirements

Conduct an in vitro study to characterize and quantify the degradants of immediate release omeprazole of Yosprala at various pH ranges (i.e., pH 1, 1.5, 2, 2.5, 3, 3.5, 4) following a minimum of 1 hour of exposure at 37°C, and evaluate the differences in the profiles. Submit the chromatograms and a summary of quantitative data generated during the study.

Final Protocol Submission:	11/15/2016
Study/Trial Completion:	02/01/2017
Final Report Submission:	04/01/2017

Conduct a clinical PK study evaluating the systemic exposures of the omeprazole degradants that are shown to be present at a higher level at pH <3.0 compared to higher pHs in the in vitro studies. This (b) (4) include both Yosprala and the reference product for the omeprazole component of Yosprala. Compare the individual omeprazole degradant exposures between the two products.

Final Protocol Submission:	09/01/2017
Study/Trial Completion:	01/01/2018
Final Report Submission:	04/01/2018

I would appreciate a confirmation of receipt of this correspondence. Thank you.

V/R,

mi²

Mimi T. Phan, Pharm.D.
CAPT, U.S. Public Health Service
SR Program Management Officer
FDA/CDER/OND/ODEIII/DGIEP
10903 New Hampshire Ave
WO22, Room 5236
Silver Spring, MD 20993
Office: 301-796-5408

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/s/

MIMI T PHAN
09/01/2016

From:	Phan, Mimi
To:	Peggy Berry
Cc:	Phan, Mimi
Subject:	RE: NDA 205103 Yosprala bottle labels
Date:	Tuesday, August 30, 2016 3:54:50 PM

Ms. Berry,
Please assist and change "delayed release tablets" to "delayed-release tablets" on all the container labels to be consistent with the PI

R,

mi²

Mimi T. Phan, Pharm.D.
CAPT, U.S. Public Health Service
FDA/CDER/OND/ODEIII/DGIEP
Office: 301-796-5408

From: Peggy Berry [mailto:pberry@aralez-contractor.com]
Sent: Wednesday, August 24, 2016 11:03 AM
To: Phan, Mimi
Cc: Chung, Mary
Subject: NDA 202103 bottle labels

Hi Mimi,
Attached are the bottle labels revised with FDA comments. The official submission will be sent through the Gateway. Let me know if you need anything else.

With these final drafts and the PI and Medguide, should we expect more FDA comments or is it likely that these were all of them?

Peggy

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/s/

MIMI T PHAN
09/12/2016

From:	Phan, Mimi
To:	Peggy Berry
Cc:	Chung, Mary; Phan, Mimi
Subject:	NDA 205103 Yosprala tablet - FDA Proposed Label
Date:	Thursday, August 25, 2016 3:36:42 PM
Attachments:	NDA 205103 Yosprala Tablet FDA Proposed PI 20160825 Clean Copy.docx NDA 205103 Yosprala Tablet FDA Proposed PI 20160825 Clean Copy.pdf NDA 205103 Yosprala Tablet FDA Proposed PI 20160825 Track Changes.docx NDA 205103 Yosprala Tablet FDA Proposed PI 20160825 Track Changes.pdf NDA 205103 Yosprala Tablet FDA Proposed MG 20160825 Clean Copy.docx NDA 205103 Yosprala Tablet FDA Proposed MG 20160825 Clean Copy.pdf NDA 205103 Yosprala Tablet FDA Proposed MG 20160825 Track Changes.docx NDA 205103 Yosprala Tablet FDA Proposed MG 20160825 Track Changes.pdf

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Dear Ms. Berry

Reference is made to your New Drug Application (NDA) 205103 for Yosprala™ (aspirin/omeprazole) Delayed-Release Tablets, to the Re-Submission dated March 14, 2016.

On August 24, 2016, (with email courtesy copy on August 19, 2016) we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI, Medguide). We request to receive your resubmission of proposed PI and Medguide for NDA 205103 Yosprala both in tracked changes and clean copy, each in PDF and Word format, that addresses these issues by August 29, 2016.

For the tracked changes version of the PI and Medguide to be submitted in response to FDA comments:

- Please accept all FDA proposed edits as clean, and annotate your proposed revisions in tracked changes, in Word format
- In addition to tracking your proposed edits, this version should also track all comment balloons, both FDA's and Sponsor's responding comments, along the right margin in Word format.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please confirm receipt of this correspondence and please submit your response to the

application. Thank you.

V/R,

mi²

Mimi T. Phan, Pharm.D.
CAPT, U.S. Public Health Service
SR Program Management Officer
FDA/CDER/OND/ODEIII/DGIEP
10903 New Hampshire Ave
WO22, Room 5236
Silver Spring, MD 20993
Office: 301-796-5408

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

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/s/

MIMI T PHAN
09/01/2016

From:	Chung, Mary
To:	Peggy Berry
Cc:	Phan, Mimi; Chung, Mary
Subject:	NDA 205103 Yosprala (aspirin/omeprazole) - container label
Date:	Wednesday, August 17, 2016 9:42:15 AM

Hello Peggy,
Reference is made to your March 14, 2016 resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin and omeprazole) delayed-release tablets, 81 mg/40 mg and 325 mg/40 mg.

We have the following comments to your container labels. We request you resubmit labeling that addresses these issues by August 24, 2016.

1. As currently presented, the proprietary name is difficult to read (b) (4) We recommend that you increase the prominence of the proprietary name to improve readability.
2. We recommend that you include a space between the numerical strength and unit of measure (e.g. 81 mg/40 mg vs. 81mg/40mg) as the letter "m" can be confused for a zero or two zeros.
3. Consider combining the two dosage statements on the left and right of the principal display panel to the following statement: "Usual dose: Take 1 tablet daily at least 60 minutes before a meal. Tablet should be swallowed whole with liquid."

Regards,
Mary

Mary Chung, PharmD.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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/s/

MARY H CHUNG
08/17/2016

From:	Phan, Mimi
To:	Peggy Berry
Cc:	Chung, Mary; Phan, Mimi
Subject:	RE: NDA 205103 Yosprala CMC Information Request
Date:	Wednesday, August 10, 2016 3:12:00 PM

Greetings Ms. Berry,

Reference is made to your resubmission of New Drug Application (NDA) 205103 Yosprala (aspirin/omeprazole) tablets dated March 14, 2016. We have an additional request, please see below:

Based on the *in vitro* omeprazole dissolution profile in 0.1 N HCl (page 27 in section 3.2.P.2, sequence 0046 in EDR), we observe a significant degradation (around (b)(4)% of label claim) of the omeprazole amount. Since PPIs are known for their chemical instability in acidic medium and omeprazole is not enteric coated in the Yosprala tablets, questions are raised regarding characterization of the degradants formed in the acidic medium of stomach and their safety. Please provide data characterizing the degradation profile of omeprazole in the stomach after administration of Yosprala tablets and address the safety of these degradants in the amounts formed.

Please confirm the receipt of this email and please submit yours response to the application by or before Noon, on Friday, August 12, 2016. Please let me know if you have additional questions. Thank you.

V/R,

mi²

Mimi T. Phan, Pharm.D.
CAPT, U.S. Public Health Service
SR Program Management Officer
FDA/CDER/OND/ODEIII/DGIEP
10903 New Hampshire Ave
WO22, Room 5236
Silver Spring, MD 20993
Office: 301-796-5408

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/s/

MIMI T PHAN
09/12/2016

From:	Phan, Mimi
To:	Peggy Berry
Cc:	Phan, Mimi; Chung, Mary
Subject:	NDA 205103 Yosprala Clinical Pharmacology Information Request
Date:	Wednesday, July 13, 2016 4:05:43 PM

Greetings Ms. Berry,

Reference is made to your resubmission of New Drug Application (NDA) 205103 Yosprala (aspirin/omeprazole) tablets dated March 14, 2016. We have an additional request, please see below:

In the submission for NDA 205103, you have not compared the exposure of omeprazole from PA8140 directly with Prilosec 40 mg. We acknowledge that you have compared the exposure of omeprazole from PA32540 with Prilosec 40 mg in study PA32540-112 on Day 1, 5 and 7 (also in study PA32540-113 only on Day 1) and compared the exposure of omeprazole from PA32540 to that of PA8140 in study PA8140-103 on Day 7 only. Using the available cross-study data, please provide us the estimated geometric mean ratio and its corresponding confidence interval comparing Cmax and AUC of omeprazole from PA8140 to Prilosec.

Please confirm the receipt of this email and Please submit yours response to the application by Noon, on Friday, July 15, 2016. Please let me know if you have additional questions. Thank you.

V/R,

mi²

Mimi T. Phan, Pharm.D.
CAPT, U.S. Public Health Service
SR Program Management Officer
FDA/CDER/OND/ODEIII/DGIEP
10903 New Hampshire Ave
WO22, Room 5249
Silver Spring, MD 20993
Office: 301-796-5408

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/s/

MIMI T PHAN
07/13/2016

Strongin, Brian K

From: Strongin, Brian K
Sent: Tuesday, June 07, 2016 1:03 PM
To: pberry@aralez.com
Cc: Strongin, Brian K
Subject: FW: seq 49 for NDA 205103

Please submit a clean copy of the package insert ASAP. Thanks.

-----Original Message-----
From: Peggy Berry [mailto:pberry@aralez.com]
Sent: Friday, June 03, 2016 9:14 AM
To: Strongin, Brian K
Subject: seq 49 for NDA 205103

Hi Brian,
Here's a copy of our response to your letter regarding the label. Let me know if you need anything else.

Peggy

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/s/

BRIAN K STRONGIN
06/07/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205103

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

POZEN Inc.
521 Andria Ave.
Hillsborough, NJ 08844

ATTENTION: Peggy Berry
Regulatory Affairs Consultant

Dear Ms. Berry:

Please refer to your New Drug Application (NDA) dated and received, March 14, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Aspirin and Omeprazole Delayed-release Tablets, 325 mg/40 mg and 81 mg/40 mg.

We also refer to your correspondence, dated and received March 15, 2016, requesting review of your proposed proprietary name, Yosprala.

We have completed our review of the proposed proprietary name, Yosprala and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 15, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, (301) 796-5295. For any other information regarding this application, contact Brian Strongin, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
05/27/2016

Strongin, Brian K

From: Strongin, Brian K
Sent: Thursday, May 12, 2016 7:01 PM
To: pberry@aralez.com
Cc: Strongin, Brian K
Subject: Yosprala Labeling IR

The Prescribing Information (PI) and Medication Guide (MG) for Prilosec was updated February 2016. See the current version here: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022056s018lbl.pdf.

Please update the format and content of the omeprazole-related information in the Yosprala PI and MG using the Prilosec PI and MG as a model, as appropriate. In particular in the Yosprala PI, please follow the new table format for omeprazole drug interactions, as found in Section 7 Drug Interactions of the Prilosec PI. Incorporate drug interactions related to the aspirin-component of Yosprala into the omeprazole table format.

In addition, we request that you revise Section 8.1 Pregnancy and Section 8.3 Nursing Mothers of the Yosprala PI to comply with PLLR. On June 30, 2015, the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. As your NDA was pending on that date, compliance with PLLR is voluntary at this time; however, we highly encourage you to comply.

For the omeprazole component of Yosprala, please follow the Prilosec PI, which has already been converted to PLLR. For the aspirin-component of Yosprala please submit the following by June 2, 2016.

• a review and summary of all available published literature regarding [aspirin] use in pregnant and lactating women,
• a review and summary of relevant cases reported in your pharmacovigilance database,
• revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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/s/

BRIAN K STRONGIN
05/13/2016

Strongin, Brian K

From: Strongin, Brian K
Sent: Tuesday, April 26, 2016 12:01 PM
To: pberry@aralez.com
Cc: Strongin, Brian K
Subject: Action Items and Responses to Yosprala Follow-up Questions from the 4/18/16 T- Con

Here are our comments on your synopsis and our responses to your follow-up questions from the 4/18/16 t-con:

We suggest revising your synopsis in the second paragraph to: "As a synopsis, our action items from the meeting are that Pozen will formally submit a complete CSR and all associated data for BE study # PA32540-119 (325/40 mg tablet) through the appropriate portal during the week of
May 2, 2016. According to the sponsor, the BE study passed for both strengths and can be used to bridge changes in supplier of aspirin (b) (4), formulation and process changes."

1. **Let me know if I should also formally submit the attached minutes.**

   You may submit them to your IND or NDA.

2. **In addition, we await the written question mentioned during the call about the (b) (4) DMF (b) (4), to which we will respond expeditiously.**

   Any clarifying questions/comments will be sent cumulatively with other CMC questions in the coming weeks.

3. **Could you please advise us on the following? Pozen has been working with (b) (4) on their previous inspectional findings. At this time, we are not confident that they will have all of the necessary changes implemented during this review cycle to act as a supplier of ASA for our product submission. (b) (4) has recently been inspected by FDA (b) (4) (PAI for another sponsor) and we've been advised that there were no 483's issued. Therefore, we plan to withdrawal (b) (4) from consideration at this time and rely on (b) (4) material for approval.**

   To that end, we would plan the following:

   - **Submit an amendment that will indicate on the 356h that (b) (4) are being withdrawn from consideration as a supplier.**

   - **Update the relevant Module 3 introductory sections and specify that we are not seeking approval to use (b) (4) as a supplier at this time. The original information will remain within the body of the document for FDA review and reference purposes as it relates to (b) (4) (b) (4) BE.**

   Is this approach acceptable? Would you recommend any changes or an alternate course? Please let me know if this is adequate and/or if there are any specific additional instructions of which we should be aware.

Your proposal to withdraw [redacted] and rely on material from [redacted] is acceptable. Please update the 356h and appropriate sections of Module 3 accordingly. Provide a table clarifying the aspirin [redacted] supplier [redacted] for all supportive drug product batches.

From: Peggy Berry [mailto:pberry@aralez.com]
Sent: Thursday, April 21, 2016 9:35 AM
To: Strongin, Brian K
Subject: Follow-up

Hi, Brian.

Thank you again for organizing the call Monday April 18th, 2016 regarding the review of the Yosprala NDA (205103) resubmission. We have composed a brief "minutes" document for your consideration (attached). Let me know if I should also formally submit the attached minutes.

As a synopsis, our action items from the meeting are that Pozen will formally submit a complete CSR and all associated data for BE study # PA32540-119 (325/40 mg tablet) through the appropriate portal during the week of May 2, 2016. In addition, we await the written question mentioned during the call about the [redacted] DMF [redacted] to which we will respond expeditiously.

Could you please advise us on the following? Pozen has been working with [redacted] on their previous inspectional findings. At this time, we are not confident that they will have all of the necessary changes implemented during this review cycle to act as a supplier of ASA for our product submission. [redacted] has recently been inspected by FDA [redacted] (PAI for another sponsor) and we've been advised that there were no 483's issued. Therefore, we plan to withdrawal [redacted] from consideration at this time and rely on [redacted] material for approval.

To that end, we would plan the following:

- Submit an amendment that will indicate on the 356h that [redacted] are being withdrawn from consideration as a supplier.

- Update the relevant Module 3 introductory sections and specify that we are not seeking approval to use [redacted] as a supplier at this time. The original information will remain within the body of the document for FDA review and reference purposes as it relates to [redacted] BE.

Is this approach acceptable? Would you recommend any changes or an alternate course? Please let me know if this is adequate and/or if there are any specific additional instructions of which we should be aware.

Thank you very much!

Peggy Berry
Pozen Regulatory Lead

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/s/

BRIAN K STRONGIN
04/26/2016

Strongin, Brian K

From: Strongin, Brian K
Sent: Wednesday, March 23, 2016 11:04 AM
To: 'pberry@aralex.com'
Cc: Strongin, Brian K
Subject: FW: URGENT: NDA 205103 Yosprala Information Request from FDA

Here are our answers to your additional questions:

> FROM ORIGINAL MESSAGE … I also had a few other questions for my own planning purposes:
>
> 1. When an NDA is resubmitted, when do we normally expect a response? Is a new PDUFA date established? If so, when would we find out what the new target is?
>
>   **We have a 6 month user fee deadline from our receipt of your response to the December 16, 2014 Complete Response letter to take an action. You should receive an Acknowledgment letter in the next week or so with the new user fee deadline.**
>
> 2. Regarding the manufacturer, we are including a second manufacturer, but have not removed the original manufacturer who had issues during inspection. We know that they are working to correct their issues, but if they are unable to do it within a timely way, we will remove them from the submission. If this occurs during the review process, will it impact the submission timing at all?
>
> **If both facilities are equally capable of supporting commercial manufacture, removing one facility will not impact the review timeline.**

From: Peggy Berry [mailto:pberry@aralez.com]
Sent: Friday, March 18, 2016 5:24 PM
To: Strongin, Brian K
Cc: Brown, Anita
Subject: URGENT: NDA 205103 Yosprala Information Request from FDA

Hi Brian,
John Fort forwarded my your message about NDA 205103. I am the new contact person for Aralez, so please contact me if you need anything else. We will send in the requested information as an official submission on Monday. In the meantime, attached is the list of facilities.

In addition, I wondered if you would be able to provide answers to the questions that I previously sent to Hong? I put them below again for your convenience. Thanks for any help you can provide!

> FROM ORIGINAL MESSAGE … I also had a few other questions for my own planning purposes: When an NDA is resubmitted, when do we normally expect a response? Is a new PDUFA date established? If so, when would we find out what the new target is? Regarding the manufacturer, we are including a second manufacturer, but have not removed the original manufacturer who had issues during inspection. We know that they are working to correct their issues, but if they are unable to do it within a timely way, we will remove them from the submission. If this occurs during the review process, will it impact the submission timing at all?

Peggy Berry
Aralez Regulatory Affairs
pberry@aralez.com
302-563-4575

_____

From: Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]
Sent: Friday, March 18, 2016 10:29 AM
To: John Fort <jfort@aralez.com>
Cc: Brown, Anita <Anita.Brown@fda.hhs.gov>; Strongin, Brian K <Brian.Strongin@fda.hhs.gov>
Subject: NDA 205103 Yosprala Information Request

Please respond to the following information request ASAP.

Please update the 356h form and Section 3.2.S.2.1 with the proposed drug substance manufacturers. Each entry should include facility address, FEI, site contact person, and responsibilities. This list should be complete and include all proposed facilities for commercial manufacturing.

Thanks.

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/s/

BRIAN K STRONGIN
03/23/2016

Strongin, Brian K

From: Strongin, Brian K
Sent: Friday, March 18, 2016 10:29 AM
To: jfort@aralez.com
Cc: Brown, Anita; Strongin, Brian K
Subject: NDA 205103 Yosprala Information Request

Please respond to the following information request ASAP.

Please update the 356h form and Section 3.2.S.2.1 with the proposed drug substance manufacturers. Each entry should include facility address, FEI, site contact person, and responsibilities. This list should be complete and include all proposed facilities for commercial manufacturing.

Thanks.

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/s/

BRIAN K STRONGIN
03/22/2016

From: Strongin, Brian K
To: POssi@pozen.com
Cc: Strongin, Brian K; Griebel, Donna
Subject: FW: NDA 205103 Yosprala : alternate API site
Date: Tuesday, April 28, 2015 12:27:32 PM
Attachments: Yosprala Aspirin (b) (4) alt site (April 13).pdf

We have the following comments in response to the attachment regarding NDA 205103:

1. Chemistry, Manufacturing and Controls (CMC)

- In addition to submitting the CMC information as you proposed, you will need to provide 3 months of accelerated stability data (at least 3 time points including the initial time point) for one batch each of the final PA32540 and PA8140 tablets manufactured using aspirin (b) (4) provided by the new supplier.

2. Biopharmaceutics

- The composition of the formulation of the aspirin (b) (4) from the alternate manufacturing site contains (b) (4) In absence of BE data, provide supportive information (your own, published literature, etc.) justifying (b) (4) the bioavailability of both components (aspirin and omeprazole) of your drug product.

- You have proposed (b) (4) We do not agree with your proposal and recommend that the finished drug product containing both, aspirin and omeprazole be used in the dissolution profile comparison study supporting the addition of the alternate API manufacturing site.

3. Office of Process and Facilities/Division of Inspectional Assessment

- Ensure that all manufacturing locations are identified with full address, FEI and contact information. Specify the manufacturing operations and testing responsibilities for each facility.

- All facilities must be ready for FDA inspection at the time the new drug application is resubmitted.

Thanks and let me know if you have any questions.

From: Paul Ossi [mailto:POssi@pozen.com]
Sent: Monday, April 13, 2015 2:01 PM
To: Strongin, Brian K
Cc: Brian Downey
Subject: FW: NDA 205103 Yosprala : alternate API site

Brian, sorry to bother you…….I notice where Stacy is not available for a period of time, so I am forwarding this to you.
Thank you, Paul

From: Paul Ossi
Sent: Monday, April 13, 2015 1:56 PM
To: 'Barley, Stacy'
Cc: Brian Downey
Subject: NDA 205103 Yosprala : alternate API site

Hi, Stacy. As suggested by Mr. Godwin (Office of Compliance) in our January 28, 2015 End-of-Review meeting, POZEN is preparing to submit information to support an alternate API site for the aspirin (b) (4) component of Yosprala Tablets. Our aim is to continue pursuing the earliest possible approval of the Yosprala NDA. We anticipate that the (b) (4) issue noted in your December 16, 2014 CRL will be resolved in the coming months. However, we plan to be ready to submit an alternate site at the earliest opportunity, unless the ongoing (b) (4) issue resolves first.

I have received your previous email on February 25, 2015 about submitting an alternate API site for aspirin (b) (4) I am hoping, though, that we can obtain more specific feedback from your CMC team before we generate the required data for this submission. I have attached a brief outline of the information we plan to submit to support the alternate API site mentioned at the End-of-Review meeting. In the interest of time, it would be very helpful for us to learn by return email if the Chemistry reviewer agrees with the proposed information to be provided in the alternate API site submission. Thanks for your help.

Regards, Paul.

Paul A. Ossi
Senior Vice President, Regulatory Affairs
POZEN Inc.
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517
(919) 913-1048 (Direct)
(919) 913-1039 (Fax)

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/s/

BRIAN K STRONGIN
04/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

MEETING REQUEST GRANTED

POZEN Inc.
Attention: Paul Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yosprala.

We also refer to your December 29, 2014, correspondence requesting an end of review meeting to discuss the Complete Response (CR) letter. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The teleconference is scheduled as follows:

Date: January 28, 2015
Time: 8:00 a.m. – 9:00 a.m. EDT
Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

CDER Participants:
Division of Gastroenterology and Inborn Errors Leadership and Clinical Team Lead;
Regulatory representatives;
Compliance representatives

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

STACY R BARLEY
01/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

MEETING PRELIMINARY COMMENTS

POZEN Inc.
Attention: Paul Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole) delayed-release tablets.

We also refer to your December 29, 2014, correspondence, received December 29, 2014, requesting a meeting to discuss the December 16, 2014 Complete Response (CR) letter.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to me, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}
Stacy Barley, R.N., M.S.N., M.S.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: A
Meeting Category: End of Review Conference

Meeting Date and Time: January 28, 2015, 0800-0900 EDT
Meeting Location: Teleconference

Application Number: NDA 205103
Product Name: Yosprala (aspirin/omeprazole)
Proposed Indication: For patients who require aspirin for secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Sponsor/Applicant Name: Pozen Inc.

FDA ATTENDEES (tentative)
Division of Gastroenterology and Inborn Errors Products
Office of Compliance

SPONSOR ATTENDEES
Pozen Inc.
John Plachetka, Pharm D., Chief Scientific Officer and CEO
John Fort, M.D., Chief Medical Officer
Paul Ossi, Senior Vice President, Regulatory Affairs
Brian Downey, Regulatory Affairs Officer
Bruce Cao, Pharm. D., Director, Pharmaceutical Development

(b) (4)
TBD

Consultants
(b) (4)

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 28, 2015, from 0800-0900 EDT via teleconference between Pozen (b) (4) Consultants and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes

will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact me). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact me if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Yosprala (aspirin/omeprazole) delayed-release tablets, 81 mg/40 mg (PA 8140) and 325 mg/40 mg (PA 32540) was originally submitted March 25, 2013, as a 505(b)(2) application 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. The application was assigned as a standard review. During the review cycle, it was determined that a relative bioavailability study was needed to compare the omeprazole exposure between PA 8140 and PA 32540. A major amendment occurred thus extending the PDUFA date to April 25, 2014.

On April 24, 2014, during the inspection of the (b) (4) manufacturing facility for this application, the field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies was required before this application could be approved. Thus on April 25, 2014, the application was given a complete response (CR) action. The CR deficiencies included two items:

1) Failed facility inspection
2) Labeling deficiencies

On June 30, 2014, Pozen responded to the CR letter. On December 16, 2014, a second CR letter was issued because not all items regarding the failed facility inspection were resolved. The objective of this meeting is to discuss the CR letter.

2.0 DISCUSSION

Questions from Pozen are in plain text. Responses from the Food and Drug Administration (FDA) are in **bold** text.

Question 1.

(b) (4) has provided responses to the 483 issued April 25, 2014 including a comprehensive action plan to resolve all issues (Reference the July 1, 2014 submission). All actions have now been completed according to the stated action plan (reference the November 24, 2014 submission). What specific items, if any, have not been adequately addressed? Please identify specifically by item number and description which are outstanding and why.

FDA Response:
We are currently reviewing the information you have provided.

Question 2.
What additional information and/or what documentation must be provided, if any, and what action, if any, must be taken to resolve any remaining issue stated in your response to # 1 above.

FDA Response:
No additional information is requested at this time.

Question 3.
If CDER has not completed its review of Novacyl's responses to the April 483, what is the expected timeframe for completing the review?

a) We understand that POZEN will have to submit an NDA resubmission to reinitiate the NDA review. If no new information is required to be submitted by (b) (4) does the Division agree that such a resubmission is acceptable for review right away?
b) If additional information is required to be provided by (b) (4) what is the timeframe for review and response by Compliance once that information is submitted?

FDA Response:
We plan to be in direct communication with (b) (4) regarding the FDA inspectional findings. We will notify (b) (4) via a written communication when the review is complete and the final facility status has been determined.

Question 4.
Does the Division agree that the NDA resubmission, which will contain no substantive information, will be considered a Class 1 resubmission and be assigned a 2 month review clock?

FDA Response:
Once we receive your resubmission, we will review the content and determine if it qualifies as a Class 1 resubmission or a Class 2 resubmission [Refer to 21 CFR 314.110(b)(1)].

Class 1 and Class 2 resubmissions as defined in MAPP 6020.4:

1. **Class 1 resubmission: a complete response containing 1 or more of following: Final printed labeling or draft labeling; safety update in same format as the original safety submission with new data and changes highlighted (except where large**

amounts of new info not previously reported are presented); stability updates to support dating periods; commitments to perform postmarketing studies or proposals for such studies; assay validation data; final release testing; minor reanalysis of previously submitted data; and other minor information.

2. **Class 2 resubmission: includes any item not specified as a Class 1: any item that would require presentation to an advisory committee. A resubmission that requires a re-inspection also would be considered as a Class 2 resubmission.**

Question 5.
In light of the fact that already approved aspirin products manufactured (b) (4) are continuing to be distributed to the US market and that the 483 deficiencies are equally applicable to all aspirin products manufactured (b) (4) we seek the Division's views on whether Yosprala can be approved as a safe and effective therapy prior to final resolution of all issues raised in the 483?

FDA Response:
No. Deficiencies were communicated in the December 16, 2014, Complete Response Letter for NDA 205103 Yosprala.

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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/s/

STACY R BARLEY
01/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

MEETING MINUTES

POZEN Inc.
Attention: Paul Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole) delayed-release tablets.

We also refer to the teleconference between representatives of your firm, (b) (4) your consultants and the FDA on January 28, 2015. The purpose of the meeting was to discuss the December 16, 2014 Complete Response (CR) letter.

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

If you have any questions, call me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.S.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	End of Review Conference
Meeting Date and Time:	January 28, 2015, 0800-0900 EDT
Meeting Location:	Teleconference
Application Number:	NDA 205103
Product Name:	Yosprala (aspirin/omeprazole)
Proposed Indication:	For patients who require aspirin for secondary prevention of cardio- and cerebrovascular events in patients at risk of developing aspirin-associated gastric ulcers
Sponsor/Applicant Name:	Pozen Inc.
Meeting Chair:	Francis Godwin, MBA, Division Director (Acting), Division of Drug Quality 2, Office of Manufacturing Quality
Meeting Recorder:	CDR Stacy Barley, R.N., M.S.N., M.S.H.A., Senior Regulatory Project Manager, DGIEP

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products (DGIEP)
Donna Griebel, M.D., Director, DGIEP
Dragos Roman, M.D. Acting Deputy Director, DGIEP
Robert Fiorentino, M.D., M.P.H., Medical Team Leader, DGIEP
CDR Stacy Barley, R.N., M.S.N., M.S.H.A., Senior Regulatory Project Manager, DGIEP

Office of Compliance:
Francis Godwin, MBA, Division Director (Acting), Division of Drug Quality 2, Office of Manufacturing Quality

Office of Pharmaceutical Quality:
Zhengfang Ge, Ph.D., Chemistry Reviewer, Office of Process and Facilities (OPF)
Joseph Duran, Ph.D., Chemist, OPF (formerly Office of Compliance)
Christina Capacci-Daniel, Ph.D, Consumer Safety Officer, OPF (formerly OC)

SPONSOR ATTENDEES

Pozen Inc.

John Plachetka, Pharm D., Chief Scientific Officer and CEO
John Fort, M.D., Chief Medical Officer
Paul Ossi, Senior Vice President, Regulatory Affairs
Brian Downey, Regulatory Affairs Officer
Bruce Cao, Pharm. D., Director, Pharmaceutical Development

(b) (4)

Consultants

(b) (4)

1.0 BACKGROUND

Yosprala (aspirin/omeprazole) delayed-release tablets, 81 mg/40 mg (PA 8140) and 325 mg/40 mg (PA 32540) was originally submitted March 25, 2013, as a 505(b)(2) application 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. The application was assigned as a standard review. During the review cycle, it was determined that a relative bioavailability study was needed to compare the omeprazole exposure between PA 8140 and PA 32540. A major amendment occurred thus extending the PDUFA date to April 25, 2014.

On April 24, 2014, during the inspection of the (b) (4) manufacturing facility for this application, the field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies was required before this application could be approved. Thus on April 25, 2014, the application was given a complete response (CR) action. The CR deficiencies included two items:

1) Manufacturing facility inspection deficiencies
2) Labeling deficiencies

On June 30, 2014, Pozen responded to the CR letter. On December 16, 2014, a second CR letter was issued because not all items regarding the manufacturing facility deficiencies were resolved. The objective of this meeting is to discuss the CR letter.

FDA sent Preliminary Comments to Pozen on January 27, 2015.

2. DISCUSSION

Questions from Pozen are in plain text. Preliminary responses from the Food and Drug Administration (FDA) issued on January 27, 2015 are in **bold** text. Discussion form the January 28, 2015 teleconference is in **bold italics.**

Question 1.
(b) (4) has provided responses to the 483 issued April 25, 2014 including a comprehensive action plan to resolve all issues (Reference the July 1, 2014 submission). All actions have now been completed according to the stated action plan (reference the November 24, 2014 submission). What specific items, if any, have not been adequately addressed? Please identify specifically by item number and description which are outstanding and why.

FDA Response:
We are currently reviewing the information you have provided.

Meeting Discussion:

See meeting discussion response to question 5.

Question 2.
What additional information and/or what documentation must be provided, if any, and what action, if any, must be taken to resolve any remaining issue stated in your response to # 1 above.

FDA Response:
No additional information is requested at this time.

Meeting Discussion:

See meeting discussion response to question 5.

Question 3.
If CDER has not completed its review of (b) (4) responses to the April 483, what is the expected timeframe for completing the review?

a) We understand that POZEN will have to submit an NDA resubmission to reinitiate the NDA review. If no new information is required to be submitted by (b) (4) does the Division agree that such a resubmission is acceptable for review right away?
b) If additional information is required to be provided by (b) (4) what is the timeframe for review and response by Compliance once that information is submitted?

FDA Response:
We plan to be in direct communication with (b) (4) regarding the FDA inspectional findings. We will notify (b) (4) via a written communication when the review is complete and the final facility status has been determined.

Meeting Discussion:

See meeting discussion response to question 5.

Question 4.
Does the Division agree that the NDA resubmission, which will contain no substantive information, will be considered a Class 1 resubmission and be assigned a 2 month review clock?

FDA Response:
Once we receive your resubmission, we will review the content and determine if it qualifies as a Class 1 resubmission or a Class 2 resubmission [Refer to 21 CFR 314.110(b)(1)].

Class 1 and Class 2 resubmissions as defined in MAPP 6020.4:

1. **Class 1 resubmission: a complete response containing 1 or more of following: Final printed labeling or draft labeling; safety update in same format as the original safety submission with new data and changes highlighted (except where large amounts of new info not previously reported are presented); stability updates to support dating periods; commitments to perform postmarketing studies or proposals for such studies; assay validation data; final release testing; minor reanalysis of previously submitted data; and other minor information.**
2. **Class 2 resubmission: includes any item not specified as a Class 1: any item that would require presentation to an advisory committee. A resubmission that requires a re-inspection also would be considered as a Class 2 resubmission.**

Meeting Discussion:

No additional discussion held.

Question 5.
In light of the fact that already approved aspirin products manufactured (b) (4) are continuing to be distributed to the US market and that the 483 deficiencies are equally applicable to all aspirin products manufactured (b) (4) we seek the Division's views on whether Yosprala can be approved as a safe and effective therapy prior to final resolution of all issues raised in the 483?

FDA Response:
No. Deficiencies were communicated in the December 16, 2014, Complete Response Letter for NDA 205103 Yosprala.

Meeting Discussion:
The FDA stated that they were in "listening-mode" only during the comment given by the (b) (4) GMP expert (b) (4).

(b) (4) stated they have responded to all of the deficiencies in the 483 and asked if the FDA was reviewing all of the firm's subsequent responses to the Office of Compliance. The FDA stated that the response received within 15 business days of the inspection is being reviewed. While additional responses have been received, a thorough review of all additional responses is not required. This policy was established per a Federal Register Notice (74 FR 40211) issued on August 11, 2009. (b) (4) expressed concern and stated that they wished for all responses to be considered as part of the 483 review. FDA stated that they acknowledged the request but could not provide a definitive response to it at this time.

Pozen asked if Yosprala can be approved as a safe and effective therapy prior to final resolution of the issues raised in the 483. FDA responded, no. A recommendation of approval is based on multiple disciplinary reviews including Compliance and so the issues raised during the inspection must be adequately addressed.

The FDA noted that other facilities in (b) (4) network also manufacture similar products and asked the Sponsor to consider whether other facilities in the (b) (4) network could manufacture aspirin (b) (4) Pozen (b) (4) stated there is no alternative supply of the aspirin-(b) (4) component.

Pozen and (b) (4) stated the (b) (4) manufacturing facility was ready for inspection and offered to submit any additional information needed by the FDA. The FDA stated that they had no additional questions nor requests for any additional information at this time. The FDA stated the Office of Compliance review of the 483 and firm response is being fast tracked and they should be in communication (b) (4) soon.

Additional Discussion:
The FDA acknowledges a typo in the background section of the preliminary responses submitted to Pozen on January 27, 2015. The phrase "failed inspection" was incorrect and should be replaced by the phrase "manufacturing facility inspection deficiencies".

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of

Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There is no follow-up discussion required at this time.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
FDA/CDER/Office of Compliance to fast track (b) (4) Inspection Review	FDA	

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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/s/

STACY R BARLEY
03/02/2015

MEMORANDUM

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

DATE: November 24, 2014

TO: File of NDA 205103

THROUGH: Joette Meyer, PharmD, Acting Associate Director of Labeling, Division of Gastroenterology and Inborn Errors Products (DGIEP)

FROM: CDR Stacy Barley, R.N., M.S.N., M.H.A., Senior Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products (DGIEP)

SUBJECT: Last Round of Label Revisions for Cycle 2

APPLICATION/DRUG: NDA 205103 Yosprala

The attached version of the Prescribing Information (PI) for Yosprala (aspirin and omeprazole) delayed-release tablets consists of the clean version submitted by the Pozen (Sponsor for Yosprala) on October 31, 2014, in response to FDA comments sent on October 27, 2014, and additional revisions (displayed in track change format) proposed by the Division of Gastroenterology and Inborn Errors Products (DGIEP).

The Attached Medication Guide does not contain a final review from the patient labeling team and will be deferred to the next review cycle.

Of note, Section 12 (**Clinical Pharmacology**) of the PI consists of proposed changes by Pozen which **have not been reviewed by Clinical Pharmacology**. The proposed changes in Section 12 of the PI (which remains in Sponsors proposed track changes) will need to be reviewed by Clinical Pharmacology during the next review cycle.

The revisions made by DGIEP will need to be conveyed to Pozen during the next review cycle.

Additionally, the safety labeling language issued by way of FDAAA Safety Label Change notification letters on October 31, 2014 to the Sponsors of approved Proton Pump Inhibitors has not been included in this to-be-marketed label. This language will need to be included in the Yosprala label during the next review cycle.

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/s/

STACY R BARLEY
12/09/2014

From:	Barley, Stacy
To:	Paul Ossi (POssi@pozen.com); Brian Downey (BDowney@pozen.com)
Subject:	NDA 205103 Yosprala: labeling information request
Date:	Monday, October 27, 2014 1:40:00 PM
Attachments:	NDA 205103 Yosprala label revisions to Sponsor 10.27.docx NDA 205103 Yosprala label revisions to Sponsor 10 27.pdf

Hello Mr. Ossi and Mr. Downey,

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yosprala.

We are reviewing the label and have the following comments and information requests as noted in the attachment. Although minor formatting edits have been made, DGIEP defers comment on the content of Section 12 at this time. Do not accept your own proposed track changes.

We request a prompt written response by October 30, 2014.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.

CDR, USPHS Commissioned Corps

Senior Regulatory Project Manager

Division of Gastroenterology/Inborn Errors Products

Office of Drug Evaluation III

CDER/FDA

(301) 796-2137 (office)

(301) 796-9905 (fax)

stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
10/27/2014

From:	Barley, Stacy
To:	Paul Ossi (POssi@pozen.com)
Cc:	Brian Downey (BDowney@pozen.com)
Subject:	ND 205103 Yosprala: Labeling revisions
Date:	Friday, October 10, 2014 3:15:00 PM
Attachments:	NDA 205103 Yosprala Label revisions Cycle 2 10.10.14.docx

Hello Paul,

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yosprala.

We are reviewing the label and have the following revisions and comments as noted in the attached document.

We request a prompt written response by October 16, 2014.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.

CDR, USPHS Commissioned Corps

Senior Regulatory Project Manager

Division of Gastroenterology/Inborn Errors Products

Office of Drug Evaluation III

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stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
10/10/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205103

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

POZEN Inc.
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

ATTENTION: Paul Ossi
Senior Vice President, Regulatory Affairs

Dear Mr. Ossi:

Please refer to your NDA resubmission dated and received June 30, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Aspirin and Omeprazole Delayed-release Tablets, 325mg/40 mg and 81 mg/40 mg.

We also refer to

- Your correspondence dated and received July 17, 2013, requesting review of your proposed proprietary name, Yosprala
- Our letter dated September 13, 2013, stating that your proposed name was conditionally acceptable
- Your correspondence dated and received July 21, 2014, requesting re-review of your proposed proprietary name, Yosprala.

We have completed our review of the proposed proprietary name, Yosprala, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your July 17, 2013 and July 21, 2014, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact Stacy Barley, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
10/03/2014

From: Do, Phong
To: "POssi@pozen.com"
Subject: Information Request: NDA 205103 Submit Proprietary Name Review Request
Date: Tuesday, July 15, 2014 3:28:00 PM

Good afternoon Mr. Ossi,

This is a follow up to my message I left with your office. My name is Phong Do and I'm a project manager in the Division of Medication Error Prevention and Analysis (DMEPA). I was notified of your resubmission of NDA 205103 for aspirin/omeprazole following FDA's complete response. I had called to inform you that DMEPA is required to re-review your proprietary name in light of the complete response and the length of time since our initial conditional approval of the name Yosprala. Please submit a cover letter identifying the submission as follows: "REQUEST FOR PROPRIETARY NAME REVIEW". You may reference your original proprietary name review request of July 17, 2013 if no information has changed. The cover letter can be addressed to:

Kellie A. Taylor, Pharm.D., MPH

Deputy Director

Office of Mediation Error Prevention and Risk Management

If you have any questions, feel free to contact me.

Thank you,

Phong Do, PharmD

LCDR - USPHS

Regulatory Project Manager

FDA/CDER/OSE

Phone 301-796-4795

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/s/

PHONG DO
07/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

POZEN Inc.
Attention: Paul Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

We acknowledge receipt on June 30, 2014, of your June 30, 2014, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin and omeprazole) tablets, 81 mg/40 mg and 325 mg/40 mg.

We consider this a complete, class 2 response to our April 25, 2014 action letter. Therefore, the user fee goal date is December 30, 2014.

If you have any questions, call me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.S.H.A.
CDR/ United States Public Health Service
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

STACY R BARLEY
07/11/2014

From:	Barley, Stacy
To:	Paul Ossi (POssi@pozen.com)
Subject:	FW: NDA 205103 Yosprala: Labeling revisions
Date:	Tuesday, April 22, 2014 4:54:00 PM
Attachments:	aspirin and omeprazole (YOSPRALA) N 205103 DMPP OPDP MG Apr-2014 marked.doc aspirin and omeprazole (YOSPRALA) N 205103 DMPP OPDP MG Apr-2014 marked.pdf NDA 205103 Yosprala Label . FDA revisions 4.22.14.docx NDA 205103 Yosprala Label . FDA revisions 4.22.14.pdf

Hello Paul,

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole).

We are reviewing the label (Package Insert and Medication Guide) have made revisions as noted in the attached documents.

In addition to revising the content of the medication guide (MG), we often make significant revisions to the format of the MG as well. Therefore, it is important that Pozen use the version of the MG attached to this email as the base document for making subsequent changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

We request a prompt written response by close of business April 23, 2014, in order to continue our evaluation of your NDA.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.

CDR, USPHS Commissioned Corps

Senior Regulatory Project Manager

Division of Gastroenterology/Inborn Errors Products

Office of Drug Evaluation III

CDER/FDA

(301) 796-2137 (office)

(301) 796-9905 (fax)

stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
04/22/2014

From: Barley, Stacy
To: Paul Ossi (POssi@pozen.com)
Subject: NDA 205103 Yosprala: label information Request
Date: Friday, April 18, 2014 9:07:00 AM
Attachments: NDA 205103 Yosprala label revisions (FDA 4 18 14).docx
NDA 205103 Yosprala label revisions (FDA 4 18 14).pdf

Hello Paul,

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole).

We are reviewing the label have made revisions as noted in the attached document.

Please note, we will send you revisions to the medication guide next week.

We request a prompt written response by close of business April 21, 2014, EST in order to continue our evaluation of your NDA.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.

CDR, USPHS Commissioned Corps

Senior Regulatory Project Manager

Division of Gastroenterology/Inborn Errors Products

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stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
04/18/2014

Tran-Zwanetz, Catherine

From: Paul Ossi <POssi@pozen.com>
Sent: Monday, April 14, 2014 12:01 PM
To: Tran-Zwanetz, Catherine
Subject: RE: NDA 205103

Hi, Cathy. Again, the conditions provided in your email are acceptable to us. I left you a voice mail to this effect and also wish to know if you are also asking for a submission to confirm this, or is my email sufficient. Thanks.

Regards, Paul.

From: Tran-Zwanetz, Catherine [mailto:Catherine.TranZwanetz@fda.hhs.gov]
Sent: Monday, April 14, 2014 10:44 AM
To: Paul Ossi
Subject: NDA 205103

HI Mr. Ossi,

Per my voicemail, here is the post-marketing committee we would like you to review:

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

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
***Agreed Dissolution* Acceptance Criterion for Omeprazole for PA 325/40**	
325/40 mg: (b)(4)% in 45 minutes	

On your submission dated January 04, 2014, you proposed (b)(4) Note that the revision should also take into consideration current dissolution data from the bio batches. The new data will be

taken into consideration only if the dissolution performance is similar to that of the bio batches. These data should be submitted within 12 months of the action letter date.

Please let me know if this is acceptable and your time frame by noon today.

Thanks!
Cathy

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/s/

CATHERINE A TRAN-ZWANETZ
04/14/2014

From: Barley, Stacy
To: Paul Ossi (POssi@pozen.com)
Subject: NDA 205103 Yosprala: Labeling Information Request
Date: Friday, April 11, 2014 1:18:00 PM
Attachments: NDA 205103 Yosprala label 4 11 14 FDA revisions.pdf
NDA 205103 Yosprala label 4 11 14 FDA revisions.docx

Hello Paul,

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole).

We are reviewing the label have made revisions as noted in the attached document.

Additionally, please refer to the link below and use the labeling sample tool when correcting your formatting (particularly when revising the highlight and table of content section).

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

We request a prompt written response by close of business April 14, 2014, EST in order to continue our evaluation of your NDA.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.

CDR, USPHS Commissioned Corps

Senior Regulatory Project Manager

Division of Gastroenterology/Inborn Errors Products

Office of Drug Evaluation III

CDER/FDA

(301) 796-2137 (office)

(301) 796-9905 (fax)

stacy.barley@fda.hhs.gov

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

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/s/

STACY R BARLEY
04/11/2014

From:	Barley, Stacy
To:	Paul Ossi (POssi@pozen.com)
Subject:	NDA 205103 Yosprala Labeling revisions IR
Date:	Saturday, March 29, 2014 3:07:00 PM
Attachments:	NDA 205103 yosprala label for sponsor.docx NDA 205103 yosprala label for sponsor.pdf

Hello Paul,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole).

We are reviewing the labeling of your application and have the following requests:

Container Label and Carton Labeling:

a) Revise the presentation of the proprietary name from lowercase (i.e. yosprala) to title case where the letter 'Y' is capitalized (i.e. Yosprala) to improve readability of the name.

b) Relocate the statement "Do not split, chew, crush, or dissolve the tablet." from the side panel to the principal display panel to highlight the importance of this information.

Content of Labeling:

See revisions in the attached document. Accept all track changes to the text in which you are in agreement with. Strikeout any text in which you are not in agreement with. Ensure all changes made by you are in track change format.

We request a prompt written response by close of business April 4, 2014, EST in order to continue our evaluation of your NDA.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.

CDR, USPHS Commissioned Corps

Senior Regulatory Project Manager

Division of Gastroenterology/Inborn Errors Products

Office of Drug Evaluation III

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/s/

STACY R BARLEY
03/29/2014

Tran-Zwanetz, Catherine

From: Tran-Zwanetz, Catherine
Sent: Wednesday, March 19, 2014 2:16 PM
To: 'Paul Ossi'
Subject: NDA 205103 CMC IR

Dear Mr. Ossi,

We are reviewing the CMC section of NDA 205103, and have the following IR question:

The statistical analysis provided (f2 testing) to support the similarity between the clinical trial and the to-be-marketed formulations for the aspirin component of the PA32540 strength is not appropriate (b) (4) Therefore, reanalyze the data using multivariate analysis (refer to the dissolution guidance). Include all the input and output files generated on this analysis.

Please submit the data via email to me by noon on March 21, 2014. Please also submit the data as an amendment to your application.

If you have any questions, please contact me.

Thank you.

Cathy
301 796 3877

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/s/

CATHERINE A TRAN-ZWANETZ
03/19/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: December 6, 2013

Application Number: NDA 205103 Yosprala
Product Name: Yosprala
Sponsor/Applicant Name: Pozen

Subject: Discussion of proposed PK study

FDA Participants :
CAPT E. Dennis Bashaw, PharmD, Director, Division of Clinical Pharmacology III (DCPIII)
Sue Chih Lee, Pharm D, Clinical Pharmacology Team Lead, DCPIII
Insook kim, PharmD, Clinical Pharmacology Reviewer, DCPIII
Robert Fiorentino, M.D., Clinical Team Lead, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Stacy Barley, R.N., M.S.N., M.H.A., Senior Regulatory Project Manager, DGIEP

Sponsor/Applicant Participants :
Pozen
John Plachetka, Pharm.D. CEO and Chief Scientific Officer
John Fort, M.D. Chief Medical Officer
Paul Ossi, Regulatory Affairs

SANOFI Participants
William Daley, M.D. Medical Affairs
David Faunce, Regulatory Affairs

1.0 BACKGROUND:
NDA 205103 was submitted on March 25, 2013 for a standard review. During the review process, the review team determined a study was needed to demonstrate that the omeprazole PK profile of 8140 and 32540 are the same. Pozen agreed to do a comparative PK cross-over trial between Yosprala 8140 and 32540.

2.0 DISCUSSION: Pozen provided their proposed dates to submit the PK protocol. They proposed mid January 2014. The FDA requests the protocol sooner; preferably December 2013. Pozen plans to have the protocol reviewed by the IRB on December 20, 2013 and will submit the protocol immediately after the IRB date. Pozen will need to submit the following information formally to the application prior to the end of December: protocol, enrollment numbers, subjects, demographics, randomization, and dates in which certain segments of the study will be submitted to the FDA. Pozen is aware of the important of sending the study results by early March (March 3, 2014), as stated in Pozen's November 22, 2013, letter (received November 25, 2013). When conducting the PK study, Pozen verified they will use the same inspection sites that were recently inspected.

Pozen asked if they should still submit information regarding literature on high dose aspirin. The FDA responded yes.

3.0 ACTION ITEMS:

Sponsor to submit items as agreed above prior to the end of December.

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/s/

STACY R BARLEY
01/23/2014

Barley, Stacy

n: Holovac, Mary Ann
t: Tuesday, March 18, 2014 1:39 PM
To: Barley, Stacy
Cc: Walsh, Maria R; Bertha, Amy; Duvall, Beth A; Holovac, Mary Ann
Subject: NDA 205103 Yosprala (aspirin and omeprazole) - cleared for action - with caveats

Stacy,

We discussed this application at Monday's 505(b)(2) clearance meeting. This application is cleared for action from a 505(b)(2) perspective with the following caveats:

- [redacted] (b) (4) It was confirmed via email (attached below) from your division [redacted] (b) (4) This fact needs to be clearly documented in the administrative record and a patent certification will then not be required.
- Bridging to the omeprazole component of the proposed product needs to be addressed in the assessment. (see below email)

Please make the following changes to the draft assessment before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the ase, please let us know when the RS arrives so that we can add it anew to our clearance ueue.

- *Q2: Please include Prilosec NDA 019810 as a listed drug relied upon.*
- *Q3: Please describe how the applicant bridged to the proposed product with respect to the omeprazole component of the proposed product.*
- *Q6: Please delete the reference to Ecotrin as OTC monograph products are not considered listed products*

Please let me know if you have any questions.

Mary Ann

From: Chakraborti, Tamal K
Sent: Monday, March 17, 2014 2:06 PM
To: Walsh, Maria R; Jappar, Dilara; Fiorentino, Robert P; Lee, Sue Chih H; Griebel, Donna; Barley, Stacy; Chakder, Sushanta K
Cc: Kim, Insook; Ishihara, Richard
Subject: RE: Yosprala and b2 clearance

Maria,

ne statement is necessary. Reliance [redacted] (b) (4) is not necessary, as Pozen can get the information from published literature.

Thanks,

Tamal.

From: Walsh, Maria R
Sent: Monday, March 17, 2014 1:46 PM
To: Chakraborti, Tamal K; Jappar, Dilara; Fiorentino, Robert P; Lee, Sue Chih H; Griebel, Donna; Barley, Stacy; Chakder, Sushanta K
Cc: Kim, Insook; Ishihara, Richard
Subject: RE: Yosprala and b2 clearance

Tamal,

One more clarification. The annotated labeling cites the (b) (4) labeling to support the statement: Aspirin inhibits ovulation in rats.

Is that statement necessary for the Yosprala labeling? If so, is reliance (b) (4) necessary or can Pozen they get that information from published literature?

Maria

From: Walsh, Maria R
Sent: Monday, March 17, 2014 1:30 PM
To: Chakraborti, Tamal K; Jappar, Dilara; Fiorentino, Robert P; Lee, Sue Chih H; Griebel, Donna; Barley, Stacy; Chakder, Sushanta K
Cc: Kim, Insook; Ishihara, Richard
Subject: RE: Yosprala and b2 clearance

Thanks all. I will convey all the below information to the Committee this afternoon.

Maria

From: Chakraborti, Tamal K
Sent: Monday, March 17, 2014 1:28 PM
To: Walsh, Maria R; Jappar, Dilara; Fiorentino, Robert P; Lee, Sue Chih H; Griebel, Donna; Barley, Stacy; Chakder, Sushanta K
Cc: Kim, Insook; Ishihara, Richard
Subject: RE: Yosprala and b2 clearance

Maria,

For nonclinical, the Applicant has relied on Ecotrin® (GlaxoSmithKline, aspirin) and Prilosec® (AstraZeneca, omeprazole). There is no mention of Aggrenox for nonclinical section.

Thanks,

mal

From: Walsh, Maria R
Sent: Monday, March 17, 2014 1:01 PM
To: Jappar, Dilara; Fiorentino, Robert P; Lee, Sue Chih H; Griebel, Donna; Barley, Stacy; Chakraborti, Tamal K; Joseph, David B
Cc: Kim, Insook; Ishihara, Richard
Subject: RE: Yosprala and b2 clearance

Thanks Dilara. This is very helpful. I've added David and Tamal to respond to the first bullet below re: (b) (4) (mentioned in the annotated labeling) and ovulation in rats. Would you please confirm whether Pozen is relying for approval (b) (4) for the nonclinical section? If so, they will need to cite reliance and submit a patent certification. If it's just supportive information, then we are OK.

Thanks.

Maria

From: Jappar, Dilara
t: Monday, March 17, 2014 12:52 PM
, Walsh, Maria R; Fiorentino, Robert P; Lee, Sue Chih H; Griebel, Donna; Barley, Stacy
Cc: Kim, Insook; Ishihara, Richard
Subject: RE: Yosprala and b2 clearance

Hi Maria,

Here is the clin pharm response:

1) Pozen is relying on Ecotrin (an OTC monograph product) (b) (4) Is that correct?

   Yes, the sponsor had conducted BE studies comparing the exposure of acetylsalicylic acid from the proposed products (PA32540 and PA8140) to Ecotrin at both strength (325 mg and 81 mg).

   There is not mention of (b) (4) (NDA (b) (4)) in clin pharm studies.

2) How did Pozen bridge to omeprazole?

   The sponsor had conducted a relative bioavailability study comparing the omeprazole exposure of PA32540 to that of Prilosec 40mg.
   The sponsor has recently completed another relative BA study comparing the relative exposure of omeprazole between their own products PA32540 and PA8140.

Thanks,
Dilara

m: Kim, Insook
Sent: Monday, March 17, 2014 12:30 PM
To: Jappar, Dilara
Cc: Lee, Sue Chih H
Subject: FW: Yosprala and b2 clearance
Importance: High

Would you like to address?

From: Walsh, Maria R
Sent: Monday, March 17, 2014 12:10 PM
To: Barley, Stacy; Fiorentino, Robert P; Kim, Insook; Lee, Sue Chih H
Cc: Ishihara, Richard; Griebel, Donna
Subject: Yosprala and b2 clearance
Importance: High

The 505(b)(2) Clearance Committee will be discussing the Yosprala application today at 2:00 pm. Their questions appear below in italics. My questions are: 1) Pozen is relying on Ecotrin (an OTC monograph product) and NOT on (b) (4) NDA (b) (4) Is that correct? And 2) How did Pozen bridge to omeprazole?

1. **NDA 205103 for Yosprala (aspirin/omeprazole) tablets, 81mg aspirin; 40mg omeprazole and 325mg aspirin;40mg omeprazole**
   Applicant: Pozen, Inc.
   Action Goal Date /PDUFA Goal Date: April 24, 2014
   RPM/Div: Stacy Barley/DGIEP
   Planned Action: approval anticipated, but awaiting additional information from the sponsor
   Clearance history: new application
   Issues for discussion:
   - *The annotated labeling includes a reference (b) (4) at the top page 33 and states "Aspirin inhibits ovulation in rats." (b) (4) NDA (b) (4) listed in the Orange Book is an aspirin; (b) (4) The sponsor did not indicate reliance on the (b) (4) NDA and did not certify to the listed unexpired patent. Was the (b) (4) NDA (b) (4) relied upon?*
   - *If yes to the above question, does the committee agree that Pozen will need to address reliance upon NDA (b) (4) and submit an additional patent certification?*
   - *The assessment indicates bridging was done via bioequivalence studies between the proposed product and enteric coated aspirin and no reference is made to the omeprazole active ingredient. Does the committee agree that additional bridging information is needed?*

   Recommendation: PENDING

nks.

Maria

Maria R. Walsh, RN, MS
Associate Director for Regulatory Affairs

d and Drug Administration
er for Drug Evaluation and Research
e of New Drugs
Office of Drug Evaluation III
10903 New Hampshire Ave Bldg 22 Room 5206
Silver Spring, MD 20993-0002
Telephone: (301) 796-1017
Fax: (301) 796-9906
e-mail: maria.walsh@fda.hhs.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

REVIEW EXTENSION – MAJOR AMENDMENT

POZEN Inc.
Attention: Paul Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your March 25, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Yosprala (aspirin and omeprazole) Tablets, 81 mg/40 mg and 325 mg/40 mg.

On December 18, 2013, we received your December 18, 2013, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 25, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 28, 2014.

If you have any questions, call CDR Stacy Barley, Senior Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology & Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
12/19/2013
Signing for Donna Griebel, Director, DGIEP

MEMORANDUM

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

DATE: November 14, 2013

TO: The File of NDA 205103

THROUGH: Robert Fiorentino, M.D., M.P.H.

FROM: CDR Stacy Barley, R.N., M.S.N., M.H.A.

SUBJECT: Informal discussion of Application with Sponsor

APPLICATION/DRUG: NDA 205103 Yosprala

Background: On November 1, 2013, the Division of Gastroenterology and Inborn Errors Products (DGIEP) issued an information request to Pozen, sponsor of NDA 205103 Yosprala. The information request stated that evidence suggests that for CV protection, there is no incremental benefit in chronic administration of doses of aspirin (ASA) above 100 mg and that higher ASA doses increase the risk of major bleeding. DGIEP questioned whether patients at sufficient risk for gastric ulceration who would need chronic administration of a PPI should be administered 325 mg of aspirin due to the potential increase risk of major bleeds. Pozen was also notified that they have not conducted adequate and well-controlled trials to establish the efficacy of PA8140, although they have submitted such trials for PA32540.

Pozen responded to the information request on November 11, 2013 and a telecon was held on November 14, 2013 to discuss their response.

FDA Participants:
Donna Griebel, Robert Fiorentino, Zana Marks, Preston Dunnmon, Stephen Grant, Sudharshan Hariharan, Dilara Jappar, Insook Kim, Banu Zolnik, Sandra Suarez, Stacy Barley

POZEN Participants:
John Plachetka, Pharm.D. CEO and Chief Scientific Officer; John Fort, M.D. Chief Medical Officer; Paul Ossi, Regulatory Affairs; Bruce Cao, Pharm.D. Pharmaceutical Development; Brian Downey, M.S. Pharmaceutical Development; Ying Zhang, Biostatistics

SANOFI Participants:
Cary Yonce, Cardiovascular & Specialty Care Patient Centered Unit; Patrick Barry, Cardiovascular & Specialty Care Patient Centered Unit; William Daley, M.D. Medical Affairs David Faunce, Regulatory Affairs

Major Discussion Points:
The ACC-AHA clinical practice guidelines and monograph pertaining to the 325mg dose of aspirin was discussed. The FDA stated there is no evidence that a specific subgroup would benefit from the higher dose of aspirin. The lowest effective dose of aspirin is 81mg. Pozen can submit an argument that 325mg dose of aspirin should be made available for secondary prevention of CV events.

Pozen provided data that the dissolution of omeprazole in the PA8140 and PA32540 was in their view similar. However, the FDA reiterated that bridging efficacy based only on dissolution can not be used (b) (4)

There is no pharmacokinetic data (PK) on the PA8140 dose. FDA believed that Pozen will need to get PK data to demonstrate that the omeprazole exposures in PA8140 is similar to that in PA32540. This would support bridging of the efficacy data of PA32540 to PA8140, since one could argue that the efficacy of PA8140 should be at least as good as PA32540 under similar omeprazole exposures.

Follow-up Items:

1. Pozen will submit a document supporting their position relative to the concerns raised by the FDA relating to the 325 mg aspirin dose; and
2. FDA will provide feedback regarding the re-evaluation of the Lanza score data establishing the bridge from PA32540 to PA8140 relative to the omeprazole component.

_____
CDR Stacy Barley, R.N., M.S.N., M.H.A.

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/s/

STACY R BARLEY
12/03/2013

McKnight, Rebecca

From: McKnight, Rebecca
Sent: Thursday, November 07, 2013 10:25 AM
To: 'POssi@pozen.com'
Subject: IR Letter for NDA 205103

Dear Mr. Ossi,

We are reviewing the CMC section of NDA 205103, and wish to notify you that DMF (b) (4) continues to be deficient.

If you have any questions, please contact me.

Thank you,

Rebecca McKnight
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
CDER-ONDQA
301-796-1765

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/s/

REBECCA A MCKNIGHT
11/07/2013

From: Barley, Stacy
To: "Paul Ossi";
Subject: NDA 205103 Yosprala: Information request
Date: Monday, November 04, 2013 12:47:17 PM

Hello Paul,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole) (NDA 205103).

We need a further clarification for Question 3 from the original IR sent to you October 4, 2013, in which you responded on October 18, 2013: Stratify the primary endpoint analysis by study, treatment arm, and history of gastric or duodenal ulcer (GU/DU) within the last 5 years prior to enrollment (yes/no). **Please provide the presentation of the data across subgroups rather than the submitted stratified CMH analysis.**

Additionally, please provide the dial in information for the November 14, 2013, teleconference. We request a prompt written response by close of business November 7, 2013, in order to continue our evaluation of your NDA.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
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(301) 796-2137 (office)
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stacy.barley@fda.hhs.gov

document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.

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/s/

STACY R BARLEY
11/04/2013

From: Barley, Stacy
To: "Paul Ossi";
Subject: NDA 205103 Yosprala: IR in preparation for 11/14/13 teleconference
Date: Friday, November 01, 2013 11:16:46 AM

Hello Paul,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole).

In preparation of the upcoming teleconference scheduled for November 14, 2013, we have the following comments/requests:

Evidence suggests that for CV protection, there is no incremental benefit in chronic administration of doses of ASA above 100 mg and that higher ASA doses increase the risk of major bleeding". As you have also acknowledged in section 2.3.1.2 of your Clinical Overview, "the relevant antithrombotic effects of aspirin have been demonstrated to occur over the dose range of 50-325 mg." We also question whether patients at sufficient risk for gastric ulceration who would need chronic administration of a PPI should be administered 325 mg of aspirin due to the potential increase risk of major bleeds. Therefore PA8140 appears to be a more appropriate dose for your proposed indications.

That being said, you have not conducted adequate and well-controlled trials to establish the efficacy of PA8140, although you have submitted such trials for PA32540. In order to rely on the efficacy data from the trials conducted with PA32540 to support the efficacy of PA8140, at a minimum the review team must have evidence that the pharmacodynamic effect of the omeprazole in PA8140 that increase gastric pH are no less than that provided by the omeprazole component in PA32540. This could be established by demonstrating that omeprazole exposure from PA8140 is bioequivalent to (or greater than) that of PA32540. We note that omeprazole PK from PA8140 was not characterized in this NDA submission. However, we are concerned that the different dissolution profiles of the omeprazole component of PA32540 and PA8140 suggest a potential difference in omeprazole exposure that could be clinically relevant.

Alternatively, if there is evidence that omeprazole exposure does or could differ between PA32540 and PA8140, you would need to provide evidence that this difference is not clinically meaningful or relevant (so that reliance on the efficacy

of PA32540 could support the efficacy of PA8140). However, the review team is currently not aware of data that would provide such evidence.

N Engl J Med 2010;363:930-942
Am J Card 2005;95:1218
Circ. 2003; 108:1682-1687
BMJ. 2002;324:71-86).

Please provide your plan to address these points and/or provide data that helps resolve our concerns. You can also provide additional information or alternative proposals that support PA8140 as an effective therapy for the proposed indication. Information provided prior to the upcoming teleconference would be helpful for the discussion. Therefore, we request a response by November 12, 2013, if possible.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
11/01/2013

From: Barley, Stacy
To: "Paul Ossi";
Subject: NDA 205103 Yosprala: Information request
Date: Friday, October 11, 2013 1:11:21 PM

Hello Paul,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yosprala (aspirin/omeprazole).

We are reviewing the Clinical and Statistical sections of your application and have the following requests:

1. By study and treatment arm, tabulate the number of subjects who did not have a post-randomization endoscopy. Summarize the reasons why endoscopies were not performed in these subjects.

2. By study and treatment arm, for the subjects who did not have a post-randomization endoscopy, list each subject's duration in the study (in days).

3. By study and treatment arm, for the subject who did have post-randomization endoscopy(ies), list each subject's last endoscopy day, duration in the study (in days), and the result of the last endoscopy (ulcer or ulcer-free).

We request a prompt written response by close of business October 18, 2013, EST in order to continue our evaluation of your NDA.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
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/s/

STACY R BARLEY
10/11/2013

PeRC PREA Subcommittee Meeting Minutes
September 25, 2013

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Karen Davis-Bruno
Rosemary Addy
Patricia Dinndorf
Tom Smith
Julia Pinto
Ethan Hausman
William J. Rodriguez
Peter Starke
Wiley Chambers
Lily Mulugeta
Daiva Shetty
Andrew Mulberg
Andrew Mosholder
Martha Nguyen
Dianne Murphy
Dionna Green
Dionna Green
Jane Inglese

Guests Attending:
Renan Bonnel (OPT)
Maura Oleary (CBER)
Terrie Crescenzi (OPT)
Nichella Simms (PMHS)
Erica Radden (PMHS)
Gilbert Burckart (OCP)
Donna Snyder (PMHS)
Rohini Dave
Ruthanna Davi (OB)
Raj Nair (DPARP)
Janet Magnard (DPARP)
Jianmeng Chen (OCP)
Wendy Carter (DAVP)
Karen Winestock (DAVP)
Nina Mani (DAVP)
Stanley Au (OCP)
Karimi-Shah, Banu (DPARP)
Tracy Kruzick (DPARP)

Agenda

11:00	NDA	NON-RESPONSIVE	
	NDA		
	NDA		
	NDA		
	NDA	205103	Yosprala (aspirin/omeprazole) Full Waiver
	NDA	NON-RESPONSIVE	
	NDA		

NON-RESPONSIVE

1 Page has been Withheld in Full as Non Responsive immediately following this page

Yosprala (aspirin/omeprazole) Full Waiver

- NDA 205103 seeks marketing approval for Yosprala (aspirin/omeprazole) for secondary prevention of cerebrovascular and cardiovascular events in patients at risk of developing aspirin-associated gastric ulcers.
- The application was submitted on March 24, 2013, and has a PDUFA goal date of January 23, 2014.
- The application triggers PREA as directed to a new indication.
- A full waiver is being requested because studies are impossible or highly impractical and because the product would be ineffective and/or unsafe in pediatric patients.
- *Division justification for waiver:* The use of aspirin for the proposed indication in the pediatric population is rare, therefore the incidence of aspirin associated gastric ulcers would also expected to be rare. In addition, evidence exists that Yosprala would be unsafe in all pediatric age groups due to the aspirin component. The Division therefore concurs with the sponsor's proposed rationale for requesting a waiver from the requirement to conducting studies with Yosprala in pediatric patients from birth to 18 years of age.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical.

NON-RESPONSIVE

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/s/

JANE E INGLESE
10/07/2013

Davis, Anissa

From: Davis, Anissa
Sent: Friday, October 04, 2013 2:14 PM
To: possi@pozen.com
Cc: Barley, Stacy
Subject: NDA 205103 Yosprala: Clinical Information Request

Hello Mr. Ossi:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Yosprala PA8140 and PA32540 (aspirin/omeprazole).

We are conducting a review of the Clinical section of your submission and have the following comments and information requests:

1) For both Trials PA32540-301 and -302, present the following (separately for each trial) in tabular format:

    a. By treatment arm, tabulate the proportion of subjects who were taking 1) Cox-2 inhibitors, 2) Other NSAIDS at baseline or 3) either COX-2 inhibitors or other NSAIDS.
    b. By treatment arm, tabulate the proportion of subjects who met the primary endpoint in subjects who were taking 1) COX-2 inhibitors or 2) Other NSAIDS and 3) COX-2 inhibitors or other NSAIDS or 4) no NSAIDS and no Cox-2 inhibitors at baseline.

2) By study and treatment arm, for all patient subgroups described in Question 1, tabulate the number (n) and % of adverse reactions that occurred ≥ 2% subjects (i.e., n/N, where N is total number of subjects in study treatment arm; not the subgroup) who, 1) used NSAID *or* COX-2 inhibitors at baseline, 2) used NSAID or COX-2 use with prior or concomitant PPI at baseline and 3) used NSAID or COX-2 use without prior or concomitant PPI at baseline.

3) Stratify the primary endpoint analysis by study, treatment arm, and history of gastric or duodenal ulcer (GU/DU) within the last 5 years prior to enrollment (yes/no).

4) By study and treatment arm, tabulate the mean and median age of those individuals with GU/DU history within the last 5 years prior to enrollment.

5) Indicate whether or not alcohol use (e.g., yes/no, frequency of use, amount, etc.) was recorded at baseline and/or during the study. If such data were collected, provide analysis of adverse reactions based on alcohol usage by treatment arm and study.

6) By study and treatment arm, tabulate the reasons for discontinuation from the study for subjects who were ulcer free during the entire treatment phase. List the reasons for discontinuation, providing counts and proportions (n/N, with N defined as above) by treatment arm and study. Repeat this analysis for subgroups of age (e.g., greater/less than 55, 65), gender, and race.

7) By study and treatment arm, present the number of subjects who had erosions (or other related findings on baseline endoscopy) that were enrolled but otherwise did not meet the following exclusion criterion: Baseline endoscopy showed any gastric, esophageal or duodenal ulcer at least 3 mm in diameter with depth.

CDR Stacy Barley is currently on leave. Therefore, please provide a written response via email to the both of us by 10/18/2013. In addition, submit the information to your NDA as soon as possible.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, USPHS Commissioned Corps
Regulatory Project Manager
Food and Drug Administration/Center for Drug Evaluation and Research
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
(301) 796-5016(office)
(301) 796-9904 (fax)
Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
10/04/2013

From: Barley, Stacy
To: John Fort; "Paul Ossi";
Subject: NDA 205103 Yosprala: Clinical Pharmacology IR 9.18.13
Date: Wednesday, September 18, 2013 8:54:20 AM

Hello,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NDA 205103 Yosprala (aspirin/ omeprazole).

We are reviewing the Clinical Pharmacology section of your application and have the following request for information:

> In the bioanalytical reports for studies PA8140-102, PA32540-115, PA32540-113, PA32540-105 and PA32540-112, you have indicated that long term storage stability of acetylsalicylic acid and salicylic acid were established for 359 days at 70^{o}C. However, a bioanalytical validation report supporting such a statement was not included in any of these bioanalytical reports. Please submit or assist us locating such a bioanalytical validation report to support the long term stability of acetylsalicylic acid and salicylic acid at 70^{o}C for 359 days.

We request a prompt written response by close of business September 20, 2013, EST in order to continue our evaluation of your NDA.

Please contact me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.S.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
09/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

POZEN Inc.
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

ATTENTION: Paul Ossi
Senior Vice President, Regulatory Affairs

Dear Mr. Ossi:

Please refer to your New Drug Application (NDA) dated and received March 25, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Aspirin and Omeprazole Tablets, 81 mg/40 mg and 325 mg/40 mg.

We also refer to your correspondence, dated and received July 17, 2013, requesting review of your proposed proprietary name, Yosprala. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Yosprala will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 17, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Anissa Davis at (301) 796-5016

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
09/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

INFORMATION REQUEST

Pozen Inc.
Attention: Paul A. Ossi,
Senior Vice President Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PA8140 and PA 32540 (aspirin/omeprazole) Tablets.

We also refer to your March 25, 2013 submission.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. DMF (b) (4) for aspirin (b) (4) was found inadequate to support this NDA. Deficiencies have been communicated to the DMF holder. All the deficiencies need to be adequately addressed before this NDA can be approved.

2. To confirm specificity of method (b) (4) for purity of omeprazole by HPLC, please provide a chromatogram for omeprazole and known impurities and report the corresponding relative retention times.

3. The in-process drug product specification includes (b) (4)

4. The established name for the drug product should be changed as follows:
   Trade Name (aspirin and omeprazole) delayed release tablets

5. You have provided a carton mark-up for your patient sample. Please also provide carton mark-up for the proposed commercial products.

6. Provide bar code on carton mark-up.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
09/06/2013
Chief, Branch IV

Tran-Zwanetz, Catherine

From: Tran-Zwanetz, Catherine
Sent: Thursday, July 25, 2013 11:39 AM
To: 'possi@pozen.com'
Cc: Davis, Anissa; Barley, Stacy
Subject: NDA 205103 Information request

Hello Paul,

Here is our latest information request for the NDA listed above:

1. *Provide dissolution data (individual, mean, SD, profiles) in the proposed QC media for the PA8140 used in PA08140-101 clinical study. In addition, provide f2 values comparing the dissolution profiles of the PA8140 Clinical Trial and the To-Be-Marketed Formulation.*

2. *Provide f2 values comparing the dissolution profiles of the Phase 3 and BE and the To-Be-Marketed Formulation of PA32540. Provide dissolution data (individual, mean, SD, profiles) in the proposed QC media, including Batch 3061488R which was used in the clinical studies.*

3. *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.).*

4. *We recommend that you set the following dissolution acceptance criteria for Aspirin and Omeprazole in your proposed product. This recommendation is based on the in vitro performance of the clinical, bioequivalence and stability batches. Please submit an updated sheet of specifications reflecting these recommendations.*

   PA 8140 Tablets

   Aspirin:

   Acid Stage: NMT (b)(4)% in 2 hours

   Buffer Stage: (b)(4)

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

   Omeprazole: *Q= (b)(4)% in (b)(4) minutesdav*

   PA 32540 Tablets

   Aspirin:

   Acid Stage: NMT (b)(4)% in 2 hours

   Buffer Stage: (b)(4)

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

Omeprazole: *Q=* (b) (4) *% in 45 minutes*

Note that the recommended acceptance criterion for the omeprazole component is based on the premise that you will be submitting data supporting the discriminating ability of the dissolution method.

Please provide a formal amendment to the NDA by August 1, 2013. Please also confirm that you have received this email.

Thanks!
Cathy

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/s/

CATHERINE A TRAN-ZWANETZ
07/25/2013

Davis, Anissa

From: Davis, Anissa
Sent: Monday, June 24, 2013 12:06 PM
To: 'Paul Ossi'
Subject: RE: NDA 205103: Response to 120 day Safety Update Question and Clinical Information Request

Hello Mr. Ossi:

In regards to your 120-Day Safety Update proposal for NDA 205103 (aspirin/omeprazole) as noted below in your email dated June 20, 2013, the Agency is in agreement.

Additionally, please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for aspirin/omeprazole.

We are reviewing the Clinical section of your submission and have the following comments and information requests regarding your pediatric waiver request.

The information submitted in your waiver request is not sufficient to support a full waiver. Provide a rationale for requesting the full waiver that falls under one of these categories:

1 - necessary studies are impossible or highly impractical (because, for example, the number of patients is so small or the patients are geographically dispersed).
2 - there is evidence strongly suggesting that the drug or biologic product would be ineffective or unsafe in all pediatric age groups.
or
3 - the drug or biologic product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** it is not likely to be used in a substantial number of pediatric patients.

Because the indication is not specific for atherosclerosis, the proposed indications do not qualify for a disease specific waiver. Provide epidemiologic data to support a full waiver. If there are any safety issues with the drug that might limit use in children, that also should be noted.

There is a concern of Reye Syndrome with aspirin use in children. Address the risk of Reye Syndrome in labeling.

We request a prompt written response by July 24, 2013, in order to continue our evaluation of your NDA.

Please contact me if you have any questions. Thank you!

Anissa

Anissa Davis, RN, B.S.N., M.P.H., C.P.H.M.
CDR, USPHS Commissioned Corps
Regulatory Project Manager
Food and Drug Administration/Center for Drug Evaluation and Research
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
(301) 796-5016(office)
(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

From: Paul Ossi [mailto:POssi@pozen.com]
Sent: Thursday, June 20, 2013 3:13 PM
To: Davis, Anissa
Cc: Barley, Stacy
Subject: NDA 205103: QUESTION- 120 day Safety Update

Anissa, in about a month we will be due to submit the 120-day Safety Update for NDA 205103. I would like to get your input ahead of time to assure we are providing the appropriate information in the 120-Day Safety Update.

Since the original NDA submission for PA Tablets on March 25, 2013, POZEN has completed (b) (4) This study protocol was submitted to IND 78,747 on May 30, 2013 (Serial # 072). No other studies with PA tablets of any strength are being conducted at this time.

(b) (4)

Please let me know if this is agreeable to the review team. Thank you.

Regards, Paul.

Paul A. Ossi
Senior Vice President, Regulatory Affairs
POZEN Inc.
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517
(919) 913-1048 (Direct)
(919) 913-1039 (Fax)

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/s/

ANISSA A DAVIS
06/24/2013
on behalf of Stacy Barley

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

PROPRIETARY NAME REQUEST
UNACCEPTABLE

POZEN Inc.
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

ATTENTION: Paul Ossi
Senior Vice President, Regulatory Affairs

Dear Mr. Ossi:

Please refer to your New Drug Application (NDA) dated and received March 25, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Aspirin and Omeprazole Tablets, 81 mg/40 mg and 325 mg/40 mg.

We also refer to your correspondence, dated and received March 27, 2013, requesting review of your proposed proprietary name, (b) (4) We have completed our review of the proposed proprietary name, (b) (4) and have concluded that this name is unacceptable for the following reasons:

(b) (4)

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We note that you have proposed an alternate proprietary name in your submission dated March 27, 2013. In order to initiate the review of the alternate proprietary name, (b) (4), submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Anissa Davis at (301) 796-5016

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
06/21/2013

Davis, Anissa

From: Davis, Anissa
Sent: Friday, May 31, 2013 11:23 PM
To: possi@pozen.com
Cc: Barley, Stacy
Subject: NDA 205103 PA8140 and PA32540 (aspirin/omeprazole): Statistics IR

Hello Paul:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PA8140 and PA32540 (aspirin/omeprazole).

We are conducting a review of the Statistical section of your submission and have the following information requests:

1. Perform the following sensitivity analyses for studies PA32540-301 and PA32540-302 separately for the primary efficacy endpoint:
    a. Observed case: exclude subjects from the analysis at a specific time point if the patients have insufficient data at that time point.
    b. Worst case: (1) subjects with missing observations at any of the time points of the analysis are assumed to be non-responders; (2) subjects receiving EC-aspirin 325 mg with missing observations at any of the time points of the analysis are assumed to be responders, and subjects receiving PA32540 with missing observations at any of the time points of the analysis are assumed to be non-responders.
    c. LOCF (last-observation-carried-forward) analysis
    d. Model-based multiple imputation methods

2. Perform analysis on the cumulative proportion of subjects developing gastric ulcers, duodenal ulcers, gastric and/or duodenal ulcers at 1, 3, 6 months for studies PA32540-301 and PA32540-302 separately, where ulcer is defined as of size greater or equal to 5 mm in diameter.

3. Perform subgroup analyses on the primary efficacy endpoint by baseline ulcer size {0, (0, 1], (1, 2], and (2, 3]}.

4. Perform analysis on the time-to-develop first ulcer.

5. Provide SAS transport file**s** for the ulcer data (endoscopy analysis data) for studies PA32540-301 and PA32540-302 separately. The data sets should include the following variables:
    a. Protocol number
    b. Subject ID
    c. Site identifier
    d. Treatment group
    e. Baseline ulcer size
    f. NSAID strata at randomization
    g. ITT (yes/no)
    h. MITT (yes/no)

i. 6-month completer (yes/no)
j. Date of endoscopy – (at baseline, Month 1, Month 3, and Month 6)
k. Largest duodenal ulcer diameter – (at baseline, Month 1, Month 3, and Month 6)
l. Largest gastric ulcer diameter gastric - (at baseline, Month 1, Month 3, and Month 6)
m. Duodenal ulcer status (yes/no) - (at baseline, Month 1, Month 3, and Month 6)
n. Gastric ulcer status (yes/no) - (at baseline, Month 1, Month 3, and Month 6)
o. Completer status (yes/no) - (at baseline, Month 1, Month 3, and Month 6)
p. Evaluable status (yes/no) - (at baseline, Month 1, Month 3, and Month 6)

We request a prompt written response by June 15, 2013 in order to continue our evaluation of your NDA.

Thank you!

Anissa

Anissa Davis, RN, B.S.N., M.P.H., C.P.H.M.
CDR, USPHS Commissioned Corps
Regulatory Project Manager
Food and Drug Administration/Center for Drug Evaluation and Research
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
(301) 796-5016(office)
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Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
05/31/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

FILING COMMUNICATION

POZEN Inc.
Attention: Paul Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your New Drug Application (NDA) dated and received March 25, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (aspirin/omeprazole) tablets, 81 mg and 325 mg aspirin/ 40 mg omeprazole.

We also refer to your amendments dated March 27, 2013, April 30, 2013, and May 21, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 25, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 26, 2013.

During our filing review of your application, we identified the following potential review issues and have the following requests as applicable:

1. Provide 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 recommendations in the 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).

5. 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:

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

        - Address how the (b) (4) (b) (4) are controlled for microbial growth

6. 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.

7. Describe activities taken when microbiological acceptance criteria are not met at control points.

8. Provide an updated stability schedule to reflect the microbial limits testing (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

9. Highlights (HL): The bolded HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)." Remove the italics as well as the dosage form from the statement. Use the term TRADENAME" as a proprietary name place holder instead of "BRANDNAME".

10. Highlights (HL): All text in the product title must be bolded and not italicized. The drug name must be followed by drug's dosage form (unless the dosage form is part of the drug name) and route of administration (ROA). For example" **MYDRUG (drugozide) tablets, for oral use.**

11. Highlights (HL): If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]." Include the pharmacologic class as indicated.

12. Highlights (HL): For drug products other than vaccines, the verbatim bolded statement must be present: "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch". Provide a complete contact number for POZEN.

13. Highlights (HL): Remove the italics from the words "and Medication Guide" in the following statement:
"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."

14. Contents: Table of Contents: All subsection headings must be indented, not bolded, and in title case. The word "experience" for the subsection "6.2 Post-marketing experience" is not in title case. The word "use" in sections 5.13 and 5.15 and the word "marketing" in section 6.2 is also not in title case.

We request that you resubmit labeling that addresses these issues by June 7, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call CDR Stacy Barley, Senior Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.,
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

DONNA J GRIEBEL
05/23/2013

Davis, Anissa

From: Davis, Anissa
Sent: Friday, May 17, 2013 8:00 PM
To: possi@pozen.com
Subject: NDA 205103 PA8140 and PA32540 (aspirin/omeprazole) tablets: Clinical IR

Hello Paul:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PA8140 and PA32540 (aspirin/omeprazole).

We are conducting a preliminary review of the Clinical section of your submission and have the following information requests:

- Provide the efficacy results by clinical sites.

We request a prompt written response by May 21, 2013.

Thank you.

Anissa

Anissa Davis, RN, B.S.N., M.P.H., C.P.H.M.
CDR, USPHS Commissioned Corps
Regulatory Project Manager
Food and Drug Administration/Center for Drug Evaluation and Research
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
(301) 796-5016(office)
(301) 796-9904 (fax)
Anissa.Davis@fda.hhs.gov

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

/s/

ANISSA A DAVIS
05/17/2013

From:	Paul Ossi
To:	Davis, Anissa
Cc:	Barley, Stacy
Subject:	RE: NDA 205103 IR
Date:	Friday, May 03, 2013 3:41:56 PM
Attachments:	12-revew-guide.pdf

The requested information was included as Table E101 which was attached as an appendix to the Reviewers Guide (Module 1) in the original NDA submission. I have attached a copy to this email. Please let me know if this answers your question. Thanks, Paul.

From: Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
Sent: Friday, May 03, 2013 2:51 PM
To: Paul Ossi
Cc: Barley, Stacy
Subject: NDA 205103 IR

Hello Paul:
Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PA8140 and PA32540 (aspirin/omeprazole).

We are conducting a preliminary review of the Clinical section of your submission and have the following comments and information requests:

- In reviewing the application and the list of investigators by site, it does not include the number of subjects studied from each site. This information will be necessary for both studies 301 and 302. If this information was included in your previous submission, please provide instruction of its location. If not, please submit the subject number information by site and investigator.

We request a prompt response by **May 7, 2013** (May 10, 2013 at the latest).

Thank you.

Anissa

Anissa Davis, RN, B.S.N., M.P.H., C.P.H.M.
CDR, USPHS Commissioned Corps
Regulatory Project Manager
Food and Drug Administration/Center for Drug Evaluation and Research
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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.

Reviewer's Guide to the PA Tablets NDA 205103

NAVIGATION

As discussed with the Division of Gastroenterology Products at the April 23, 2012 pre-NDA meeting, NDA 205103 is provided herewith in eCTD format. If the reviewers have any questions about the use or navigation through this application, please call Paul Ossi at 919-913-1048 (email: possi@pozen.com), or Roxanne Loudenslager at 919-913-1084 (email: rloudenslager@pozen.com).

Documents are bookmarked and hyperlinked according to "Guidance for Industry Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications – June 2008 Electronic Submissions Revision 2."

Draft labeling is provided in SPL format in accordance with "Guidance for Industry Providing Regulatory Submissions in Electronic Format – Content of Labeling – April 2005 Electronic Submissions." As requested by the Division, a word document version is provided in Module 1.14.1.3.

OTHER ADMINISTRATIVE NOTES

Please note, per guidance, if no documents have been generated for a particular section in the eCTD, no node appears in the backbone.

The terms DR, delayed release, and EC, enteric coated, are used interchangeably when referring to PA Tablets and aspirin tablets in this NDA.

For the purposes of this submission, PA8140 and PA32540 are the code names for the individual tablet strengths (81 mg and 325 mg of aspirin respectively). "PA Tablets" is used to refer to both strengths collectively and "BRANDNAME" is used in labeling in lieu of an agreed brand name.

See Notes arranged by Module below.

NOTES BY MODULE

Module 1 Administration

Submission

This submission is made through the electronic submissions gateway (ESG) and not, as proposed at the April 23, 2012 pre-NDA meeting, on DVD. This eCTD NDA will be forwarded through the gateway by POZEN's agent, (b) (4) In addition to appearing in the electronic submission, the Cover Letter and all forms with original signatures are also provided in hard copy in the blue archival binder.

Module 1.3.4 Form FDA 3454: Financial Certification

The list of Investigators attached to Form 3454 lists all Investigators, including Investigator sites that received initial study payment but who never enrolled any subjects.

Labeling

As no proprietary name has been cleared by the Agency, product labeling and packaging currently utilizes "BRANDNAME" when referring to the product.

POZEN submitted to IND 78,747 a Request for Proprietary Name review on January 23, 2013, Serial #069. In a telephone conversation between Paul Ossi of POZEN and Phong Do of FDA (DMEPA) on February 19, 2013 it was agreed that POZEN would withdraw the request from the IND and submit it as part of the NDA (i.e. Sequence 001).

Please note that multiple sections of the BRANDNAME Package Insert (PI) (Module 1.14.1) have been abstracted directly from the respective sections of the currently approved aspirin professional labeling (21 CFR 343.80) or Prilosec® Prescribing Information and are annotated directly to those documents. Sections of the proposed PI for which new data have either been generated as part of the development program or for which there is updated information that has prompted a change to the original wording, have been annotated accordingly.

Module 2 Summary

There are no specific nonclinical studies to support PA Tablets. Accordingly, no nonclinical information is provided in Module 2.6, Nonclinical Written and Tabulated Summaries. In accord with an agreement with the Division, a full review and summary of the pertinent non-clinical literature is provided in Module 2.4.

Module 3 Quality

This submission contains manufacturing data to support 2 strengths of PA Tablets, PA8140 (containing 81 mg EC-aspirin and 40 mg IR-omeprazole) and PA32540 (containing 325 mg EC-aspirin and 40 mg IR-omeprazole).

Module 4 Nonclinical Study Reports

There are no specific nonclinical studies to support PA Tablets. Copies of the publications cited in Module 2.4 literature review are included in Module 4.3.

Module 5 Clinical

Clinical Study Reports

This NDA contains a final Clinical Study Report (CSR) for each clinical study conducted with PA Tablets. There are currently no ongoing or incomplete studies to report.

Study PA325-101 in Module 5.3.4.1 was processed as a legacy document. The clinical study report and Appendices 16.1.1 through 16.1.12 appear as a single, complete document and not as eCTD granular documents. Appendices 16.3 (CRFs) and 16.4 (Data) for this study were processed separately.

All other studies are presented in accordance with the Agency guidance document for electronic submissions.

For Study PA32540-115, following an August 21, 2012 teleconference with the Agency, POZEN prepared a report addendum to include additional data analyses based on the feedback received from the Agency.

NOTE: Added information: Listings of gastric ulcer results by investigator and population from Studies 301 and 302 are provided as an attachment to this review guide (Table E101). *This listing is being provided because the Division asked for this same breakout when reviewing previous NDA 22-511 for VIMOVO Tablets which contained very similar gastric ulcer studies.*

PA Tablet Strengths

Studies PA08140-101 and PA8140-102 included PA8140 Tablets containing EC-aspirin 81 mg and IR-omeprazole 40 mg.

Studies PA325-101 and PA325-102 included PA32520 Tablets containing EC-aspirin 325 mg and IR-omeprazole 20 mg.

All other studies included PA32540 Tablets containing EC-aspirin 325 mg and IR-omeprazole 40 mg.

The pivotal efficacy and safety studies PA32540-301 and PA32540-302 also employed PA32500 Tablets containing EC-aspirin 325 mg and with an inactive film coat as a blinded comparator.

Data

Following the agreement with the Division at the pre-NDA meeting, POZEN has provided electronic SAS transport files (.xpt) with definition tables for all clinical studies.

IMPORTANT: to review the SAS transport files using SAS Viewer version above 8.2 it may be necessary to click on a number in the "Obs" column under the Library tab to bring up the full dataset.

CRFs and Annotated CRFs

All CRFs contain Electronic Signature and Combo Box Option pages. Some of the pages are of non-standard size. However, there is no loss of data and all pages are clear and legible.

Phase 1 study subject numbers are listed on the screening page/bookmark and do not appear on page 1 of these CRFs. Phase 3 study subject numbers appear on the first page of the CRF.

All bookmarks for CRFs from all studies use the study/site/subject number convention.

Table E101
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-301	390	9	1	11	1
PA32540-301	397	4	0	4	1
PA32540-301	398	1	0	2	0
PA32540-301	455	3	0	6	0
PA32540-301	479	12	0	9	1
PA32540-301	490	2	0	2	1
PA32540-301	509	9	0	8	0
PA32540-301	512	1	0	0	0
PA32540-301	530	0	0	4	0
PA32540-301	535	3	0	3	0
PA32540-301	545	2	0	1	0
PA32540-301	546	5	0	7	0
PA32540-301	549	3	0	2	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-301	602	1	0	0	0
PA32540-301	607	2	0	2	0
PA32540-301	609	1	0	2	0
PA32540-301	611	1	0	0	0
PA32540-301	635	8	0	11	0
PA32540-301	639	1	0	2	0
PA32540-301	644	4	1	7	0
PA32540-301	647	16	1	14	2
PA32540-301	648	2	0	4	0
PA32540-301	652	8	0	11	3
PA32540-301	653	1	0	0	0
PA32540-301	670	0	0	1	0
PA32540-301	677	2	0	2	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-301	680	6	0	3	0
PA32540-301	683	1	0	0	0
PA32540-301	686*	5	1	3	0
PA32540-301	696	5	1	3	1
PA32540-301	698	3	0	0	0
PA32540-301	709	1	1	4	1
PA32540-301	743	5	0	5	0
PA32540-301	745	1	0	1	0
PA32540-301	748	1	0	0	0
PA32540-301	749	5	0	6	3
PA32540-301	750	2	0	5	0
PA32540-301	764	1	0	2	0
PA32540-301	767	1	0	0	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-301	771	12	1	8	0
PA32540-301	774	2	0	0	0
PA32540-301	776	16	0	15	1
PA32540-301	777	1	0	0	0
PA32540-301	780	5	0	4	0
PA32540-301	781	1	0	2	0
PA32540-301	791	2	0	4	0
PA32540-301	792	4	0	6	0
PA32540-301	793	5	1	5	0
PA32540-301	794	5	0	5	2
PA32540-301	808	1	0	0	0
PA32540-301	812	0	0	1	0
PA32540-301	815	2	0	2	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-301	816	4	1	6	0
PA32540-301	818	2	0	0	0
PA32540-301	819	0	0	1	0
PA32540-301	824	6	0	3	0
PA32540-301	832	2	0	0	0
PA32540-301	834	3	0	1	0
PA32540-301	835	1	0	0	0
PA32540-301	840	2	0	1	0
PA32540-301	841	7	0	6	3
PA32540-301	846	6	0	4	0
PA32540-301	851*	0	0	1	1
PA32540-301	855	1	1	4	0
PA32540-301	856	8	0	7	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-301	858	1	0	0	0
PA32540-301	867	1	0	0	0
PA32540-301	870	1	0	2	0
PA32540-301	872	2	0	2	0
PA32540-301	873	1	0	1	0
PA32540-301	878	3	0	4	0
PA32540-301	879	2	0	2	0
PA32540-301	881	5	0	6	0
PA32540-301	885	3	0	3	0
PA32540-301	887	5	0	4	1
PA32540-301	888	1	1	3	1
PA32540-301	889	2	0	3	1
PA32540-301	891	2	0	2	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-302	213	0	0	1	0
PA32540-302	375	1	0	3	0
PA32540-302	379	2	0	3	0
PA32540-302	388	0	0	1	0
PA32540-302	418	0	0	1	0
PA32540-302	431	1	1	1	0
PA32540-302	438	2	0	2	1
PA32540-302	441	1	0	3	0
PA32540-302	445	4	0	1	0
PA32540-302	453	1	0	1	0
PA32540-302	478	5	0	4	2
PA32540-302	489	7	0	10	0
PA32540-302	499	11	0	9	1

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-302	501	2	0	4	0
PA32540-302	505	4	0	3	1
PA32540-302	515	1	0	2	0
PA32540-302	517	3	1	3	2
PA32540-302	551	2	0	2	0
PA32540-302	554	2	0	0	0
PA32540-302	572	9	0	12	0
PA32540-302	597	0	0	1	0
PA32540-302	598	0	0	2	0
PA32540-302	604	4	0	1	0
PA32540-302	655	11	0	9	0
PA32540-302	656	2	0	3	0
PA32540-302	657	2	0	4	1

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-302	659	1	0	1	0
PA32540-302	660	3	0	2	0
PA32540-302	662	5	0	8	2
PA32540-302	664	6	0	9	0
PA32540-302	665	0	0	2	0
PA32540-302	668	4	0	6	0
PA32540-302	669	0	0	1	0
PA32540-302	671	11	0	11	0
PA32540-302	675	7	0	4	0
PA32540-302	676	5	0	4	1
PA32540-302	687	4	0	1	0
PA32540-302	693	2	0	3	0
PA32540-302	694	9	0	7	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-302	695	4	0	1	0
PA32540-302	700	10	0	10	2
PA32540-302	754	2	0	0	0
PA32540-302	757	2	0	4	0
PA32540-302	762	0	0	3	0
PA32540-302	768	6	2	4	1
PA32540-302	773	7	2	4	0
PA32540-302	783	2	0	0	0
PA32540-302	784	5	0	6	0
PA32540-302	787	0	0	3	0
PA32540-302	796	5	0	7	0
PA32540-302	799	2	0	0	0
PA32540-302	800	2	0	2	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-302	807	1	0	0	0
PA32540-302	814	1	0	0	0
PA32540-302	825	12	1	8	1
PA32540-302	826	2	0	4	1
PA32540-302	828	0	0	1	0
PA32540-302	830	4	0	3	0
PA32540-302	837	3	0	2	0
PA32540-302	838	4	0	4	0
PA32540-302	847	9	0	8	1
PA32540-302	849	3	0	5	1
PA32540-302	850	5	0	2	0
PA32540-302	852	2	0	4	1
PA32540-302	853	5	0	3	0

* Includes subjects with gastric ulcers reported at screening.

Table E101 (Continued)
Gastric Ulcer Results by Investigator and Treatment
Intent-to-Treat Population from Studies 301 and 302

PROTOCOL NUMBER	INVESTIGATOR SITE	PA32540		EC-ASA 325mg	
		# RANDOMIZED	# GASTRIC ULCER	# RANDOMIZED	# GASTRIC ULCER
PA32540-302	854	2	0	0	0
PA32540-302	860	8	0	10	2
PA32540-302	862	4	0	6	0
PA32540-302	863	3	0	1	1
PA32540-302	871	5	0	3	0
PA32540-302	874	1	0	0	0
PA32540-302	875	1	0	0	0
PA32540-302	876	0	0	2	0
PA32540-302	883	1	0	2	0
PA32540-302	884	2	0	3	0

* Includes subjects with gastric ulcers reported at screening.

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

/s/

ANISSA A DAVIS
05/05/2013

From:	Davis, Anissa
To:	"possi@pozen.com"
Cc:	Barley, Stacy
Subject:	NDA 205103 PA8140 and PA32540 (aspirin/omeprazole)- Preliminary Regulatory Review
Date:	Friday, April 12, 2013 1:36:47 PM
Attachments:	DGIEP - Linzess (linaclotide) - format review of the prescribing informa....pdf

Hello Mr. Ossi,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PA8140 and PA32540 (aspirin/omeprazole) tablets (NDA 205103) received by the Agency on March 25, 2013. In conducting a regulatory preliminary review of your submission, we have the following comments and information requests at this time:

Form FDA 356h:

- The 356h "Dosage Form" section only states "tablets". Please clarify if the proposed product is delayed-release or not. If so, please submit a corrected 356h accordingly.
- Please review the "Cross References" information again for completeness. We noted that you mentioned in your Introduction cover letter that NDA 19810 Prilosec was also utilized as a reference listed drug (RLD) for your application. Please confirm and add the referenced Prilosec and any additional referenced application identification numbers to the "Cross Reference" section.

Form FDA 3674:

- The "Date of Certification" is the same as the "Date of the Application/Submission Which This Certification Accompanies" is the same, March 25, 2013. Please confirm if this correct?

Patent Information:

- The submitted Patent Certification lists AstraZeneca as the owner of U.S. Patent No. 6150380 and Merck as the owner of U.S. Patent Nos. 6147103. 6166213, and 6191148. Please confirm how did you obtain the information regarding Merck being the owner of the mentioned U.S. Patents.

Pediatric Study Plan (PSP):

- *Per the Food and Drug Administration Safety and Innovation Act (FDASIA), a sponsor who will be submitting an application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an initial Pediatric Study Plan (PSP) within 60 calendar days after the date of the end-of-Phase 2 meeting or such other time as may be agreed upon between the Secretary and the applicant (21 USC 355c(a) and (e))*.
    - We received your request for Pediatric Studies; however, please provide a copy of your Pediatric Study Plan (PSP), or if you have already submitted one to the Agency, please provide us with the location of the document

Please visit http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf to obtain information regarding the content requirements for the PSP.

Labeling:

- The preliminary review of your labeling information revealed errors (i.e., formatting, line spacing, etc.). The Agency reviews Sponsor submitted labels utilizing Selected Requirements of Prescribing Information (SRPI) reviews which contains 48 important PLR format regulations, guidances, and best practices. Therefore, to assist in reviewing your submitted labeling information, please review the attached publically available SRPI review for guidance and resubmit your labeling information accordingly.

We request a prompt written response by **April 19, 2013**, in order to continue the preliminary review of your NDA. Please respond to both me and Stacy Barley.

Thank you.

Anissa

Anissa Davis, RN, B.S.N., M.P.H., C.P.H.M.
CDR, USPHS Commissioned Corps
Regulatory Project Manager
Food and Drug Administration/Center for Drug Evaluation and Research
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
(301) 796-5016(office)
(301) 796-9904 (fax)
Anissa.Davis@fda.hhs.gov

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: No Format Deficiencies

Product Title	NON-RESPONSIVE
Applicant	
Application/Supplement Number	
Type of Application	
Indication(s)	
Established Pharmacologic Class[1]	
Office/Division	ODE III/DGIEP
Division Project Manager	Brian Strongin
Receipt Date	August 9, 2011
PDUFA Goal Date	September 9, 2012
SEALD Review Date	August 24, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie B. Burke

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, final agreed-upon prescribing information (PI) for critical format elements reveals **NO outstanding labeling format issues** and the SEALD Director has **NO OBJECTION** to the approval of this PI at this time.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

N/A 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

JEANNE M DELASKO
08/24/2012

LAURIE B BURKE
08/27/2012

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

/s/

ANISSA A DAVIS
04/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205103

NDA ACKNOWLEDGMENT

POZEN Inc.
Attention: Paul Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product:	PA8140 and PA32540 (aspirin/omeprazole) tablets, 81 mg and 325 mg aspirin/40 mg omeprazole
Date of Application:	March 25, 2013
Date of Receipt:	March 25, 2013
Our Reference Number:	NDA 205103

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 24, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call CDR Stacy Barley, Senior Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

ANISSA A DAVIS
04/04/2013
Signing on behalf of CDR Stacy Barley

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 78747

MEETING MINUTES

POZEN INC.
Attention: Paul A. Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PA32540 (aspirin/omeprazole) Tablets, 325 mg/40 mg.

We also refer to the teleconference between representatives of your firm and the FDA on August 21, 2012. The purpose of the meeting was to determine bioequivalence of PA32540 tablets with Ecotrin®, the reference listed drug (RLD), and the adequacy of other information that support the therapeutic equivalence for establishing the bridge to Ecotrin (RLD). You were also seeking clarification on the target indication for the proposed PA32540 tablets.

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

If you have any questions, call CDR Stacy Barley, Senior Regulatory Project Manager at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	Other
Meeting Date and Time:	August 21, 2012, 3:00 p.m. – 4:00 p.m. EDT
Meeting Location:	Teleconference
Application Number:	IND 78,747
Product Name:	PA32540 (aspirin/omeprazole) Tablets, 325 mg/40 mg.
Proposed Indication:	Secondary prevention of cardio- and cerebrovascular events and to reduce the incidence of gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers.
Sponsor/Applicant Name:	POZEN INC.
Meeting Chair:	Robert Fiorentino, M.D., M.P.H., Clinical Team Lead
Meeting Recorder:	CDR Stacy Barley, R.N., M.S.N., M.H.A., Senior Regulatory Project Manager

FDA ATTENDEES
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joyce Korvick, M.D., M.P.H., Deputy Director of Safety
Robert Fiorentino, M.D., M.P.H., Clinical Team Lead, DGIEP
Erica Wynn, M.D., M.P.H., Clinical Reviewer, DGIEP
Sue Chih Lee, Ph.D. Clinical Team Leader, Division of Clinical Pharmacology (DCP) 3, Office of Clinical Pharmacology (OCP)
Stephen Grant, M.D., Deputy Director, Division of Cardiovascular and Renal Products
Rajnikanth Madabushi, Ph.D., Clinical Pharmacology Team Lead, DCP 1, OCP
Sudharshan Hariharan, Ph.D, Clinical Pharmacology Reviewer, DCP1, OCP
Kareen Riviere, Ph.D., Biopharmaceutics Reviewer, ONDQA
CDR Stacy Barley, R.N., M.S.N., M.H.A., Senior Regulatory Project Manager, DGIEP

SPONSOR ATTENDEES
John Plachetka, Pharm. D., Chief Scientific Officer and CEO
John Fort, M.D., Chief Medical Officer
Paul Ossi, Senior Vice President, Regulatory Affairs
Lisa Zimmerman, Vice President, Clinical Operations
Ying Zhang, Director, Biostatistics

Bruce Cao, Pharm.D., Director, Pharmaceutical Development
(b) (4) Clinical Pharmacology Consultant
(b) (4) Consultant, (b) (4)
(b) (4) Consultant, (b) (4)

1.0 BACKGROUND

On April 23, 2012, a type B pre-NDA meeting was held between Pozen and the Division of Gastroenterology and Inborn Errors Products. The original NDA for PA32540 Tablets is scheduled for submission the fall of 2012.

Pozen Inc. request a Type A meeting to discuss the use of acetylsalicylic acid and/or salicylic acid to determine bioequivalence of PA32540 tablets with Ecotrin®, the reference listed drug (RLD), and the adequacy of other information that support the therapeutic equivalence for establishing the bridge to Ecotrin (RLD). They are also seeking clarification on the target indication for the proposed PA32540 tablets.

Pozen stated all studies previously discussed with the FDA in support of a 505(b)(2) application for PA8140 and PA32540 (aspirin/omperazole) Tablets have been completed.

2. DISCUSSION

Questions from POZEN are in plain text. The preliminary FDA responses sent to POZEN on August 20, 2012, are in **bold text**. The discussion held during the industry meeting between the FDA and Pozen on August 21, 2012, is in ***bold italics*** text.

QUESTIONS AND RESPONSES

1. Does the Agency agree based on the information provided in Attachment 1, and subject to confirmation after review of the totality of the data in the NDA, that sufficient information will have been provided to reasonably support establishment of the bridge to Ecotrin (RLD) as a basis for a Section 505(b)(2) application?

POZEN Position:

- Bioequivalence (BE) between PA32540 and Ecotrin 325 mg based on acetylsalicylic acid (ASA) has been demonstrated in Study PA32540-115
- PA32540 and Ecotrin 325 mg are also bioequivalent based on salicylic acid (SA)
- Equivalence between PA32540 and Ecotrin 325 mg based on PK parameters of ASA is supported by analysis of pooled data from 4 crossover pharmacokinetic studies
- Results of bioequivalence analyses are supported by pharmacodynamic studies comparing the effects of PA32540 and Ecotrin 325 mg on platelet aggregation; additionally literature data supports that the antithrombotic effects of aspirin occur over a wide dose range.
- ASA is a sub-optimal analyte and it is logistically difficult to define an accurate PK characterization suitable for evaluating bioequivalence between enteric-coated (EC) formulations of aspirin.

FDA Response

Please also see our response to Question 2, below.

- **The Agency believes that acetylsalicylic acid and not salicylic acid should be the analyte used to demonstrate bioequivalence between the FDC and Ecotrin, since acetylsalicylic acid is the active moiety for secondary prevention.**

- **The justification provided (b) (4) (b) (4) is unacceptable**

  Therefore, we do not agree that bioequivalence has been demonstrated between PA32540 and Ecotrin 325 mg in Study PA32540-115 with respect to acetylsalicylic acid.

- **Nonetheless, other available information such as the dose-response relationship of aspirin may support the establishment of a bridge between PA32540 and Ecotrin 325 mg for submission under the 505(b)(2) provision. A final decision will be made during the NDA review.**

Additional Discussion:

No additional discussion.

2. Does the Agency agree based on the information provided in Attachment 2, (b) (4) (b) (4) ?

POZEN Position:

(b) (4)

FDA Response

No. We do not agree (b) (4) **for the following reasons:**

(b) (4)

Additional Biopharmaceutics Comments

We have the following comments regarding the dissolution information that should be provided in your NDA.

1) **Dissolution Test: Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:**
    a. **Solubility data for the drug substance covering the pH range;**

b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;

c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and

d. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent; and

e. Include the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

2) Dissolution Acceptance Criteria: For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

a) The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).

b) Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).

c) Delayed release (enteric coated) products should have specifications established in both, acid stage and buffer stage per USP.

- ***Acid Stage: No individual tablet exceeds 10% dissolved at 2 hours.***
- ***Buffer Stage-IR: For immediate release, the selection of the specification time point should be where Q= (b) (4)% dissolution/release occurs.***

d) The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

Note that the dissolution method and acceptance criteria are product specific and therefore you may use any published USP or FDA method, as long it is supported with adequate dissolution profile data showing its discriminating capability for your

proposed product. In addition, note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

3) **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, we recommend that you 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).**

Additional Discussion:

(b) (4)

(b) (4) (b) (4)

Pozen will submit a request for a type A meeting to discuss literature evidence available to establish that 81 mg of aspirin is associated with a risk for ulcers and GI bleeding. They will include in that submission the steady-state PK data that demonstrates that their omeprazole 40 mg provides systemic exposure similar to the 20 mg delayed-release product. Pozen will submit CMC questions regarding minimum stability data needed to support filing of the application. They target submitting a full NDA (including both the 325mg and 81mg aspirin products) in March of 2013.

3. Does the Agency agree that the proposed indication listed below is appropriate for PA32540 and PA8140 Tablets based on previous agreements, the current monograph for Ecotrin® and other aspirin containing products and on other supporting information provided in Attachment 3?

POZEN Position:

- The application for PA32540 and PA8140 Tablets will be made under Section 505(b)(2)

of the FD&C Act based on Ecotrin as the reference listed drug (RLD)

- The Agency have previously agreed that the cardiovascular and cerebrovascular indications and dosing recommendations for the aspirin component would be supported by demonstration of equivalence to the RLD
- POZEN is not aware of any controlled studies in the literature, and there is no evidence from the current program, that indicate that the dosing recommendations currently approved in the monograph do not adequately describe the safe and efficacious use of aspirin products.

FDA Response

DGIEP believes that if only the PA32540 product is available, the indication should be restricted to the population within the ASA monograph for which this dose is indicated, i.e. patients post-CABG (b) (4)

However, if both the PA32540 and PA8140 are available, then the indication could include other populations described within the ASA monograph. The dosage and administration section would reflect the ASA monograph.

Additional FDA Comments:

We have the following recommendations for your consideration in establishment of a bridge between PA8140 and Ecotrin 81 mg.

1. **We note that plasma acetylsalicylic acid concentrations were measurable after administration of 25 mg aspirin in an immediate release formulation (e.g., Aggrenox® labeling). Nonetheless, data are currently unavailable for us to assess the bioanalytical feasibility of acetylsalicylic acid measurement in plasma after administration of delayed-release aspirin product at an 81 mg dose. A single dose administration of multiple tablets, e.g. 2-3, may be considered to increase plasma concentration of acetylsalicylic acid for the PK analysis. Since use of multiple tablets will increase the omeprazole dose beyond those approved for indications related to GERD and ulcer healing, we recommend that this study be conducted in CYP2C19 extensive metabolizers only to avoid exceptionally high systemic exposure of omeprazole, as expected in CYP2C19 poor metabolizers.**

2. **As noted previously,** (b) (4) **you will need to perform additional PK studies. However, as observed in Study PA32540-115, the mean AUC and C_{max} of acetylsalicylic acid following administration of PA32540 was about 10 - 15% lower when compared to Ecotrin 325 mg. By extrapolating this observation to PA8140, an approximately 10-15% lower systemic exposure to acetylsalicylic acid compared to Ecotrin 81 mg can be expected. It is possible that this may result in failure to demonstrate BA/BE of PA8140 to Ecotrin 81mg. Therefore, you may consider increasing the aspirin content in the lower strength of your fixed dose combination. For example, you**

could formulate "PA9040" (i.e., with 90 mg aspirin) to compensate for any potential lower systemic exposure of acetylsalicylic acid following administration of your fixed dose combination compared to Ecotrin 81 mg. Of note, Ecotrin 81 mg will remain as the reference product for assessing the relative bioavailability of the aspirin component of your fixed dose combination.

Additional Discussion:

Pozen stated in regard to the proposed indications for PA Tablets, the current monograph with professional labeling for aspirin in secondary prevention (21 CRF343.80) indicates a range of aspirin doses from 50-375 mg for a broad range of cardiovascular events. Since the approved doses of aspirin for these indications include 325mg, they believe that PA32540 should have all indications for which aspirin 325 mg is within the approved dose range. Pozen stated the proposed indication for PA32540 should thus include all the secondary uses of aspirin for which 325mg could be used, and the same for PA8140.

FDA acknowledged Pozen's concerns however will postpone the discussion of the label until the full submission arrives.

Post Meeting Addendum:

Pozen had a post-meeting question regarding Additional Comment 2 above, wherein FDA stated that Pozen may consider increasing the aspirin content in the lower strength of the fixed dose combination and formulate a "PA9040" to compensate for any potential lower systemic exposure of acetylsalicylic acid following administration of the fixed dose combination compared to Ecotrin 81 mg.

Pozen stated in post-discussion communication (b) (4)

(b) (4)

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Pozen will submit a Type A meeting request for additional discussion if needed.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
NDA submission	Sponsor	Projected March 2013

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

STACY R BARLEY
09/21/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 78,747

MEETING MINUTES

POZEN INC.
Attention: Paul A. Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PA32540 (aspirin/omeprazole) Tablets.

We also refer to the telecon between representatives of your firm and the FDA on April 23, 2012. The purpose of the meeting was to discuss submission aspects concerning content and format of your proposed New Drug Application (NDA).

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

If you have any questions, call me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 23, 2012 from 3:00 p.m. – 4:00 p.m. EDT
Meeting Location:	Teleconference
Application Number:	IND 78,747
Product Name:	PA32540 (aspirin/omeprazole) Tablets
Indication:	**Secondary prevention of cardio- and cerebrovascular events and to reduce the incidence of gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers.**
Sponsor/Applicant Name:	Pozen
Meeting Chair:	Robert Fiorentino
Meeting Recorder:	Stacy Barley

FDA ATTENDEES
Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew Mulberg, M.D., F.A.A.P., Deputy Director, DGIEP
Joyce Korvick, M.D., M.P.H., Deputy Director of Safety
Robert Fiorentino, M.D., M.P.H., Clinical Team Lead, DGIEP
Insook Kim, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) 3, Office of Clinical Pharmacology (OCP)
Sudharshan Hariharan, Ph.D., Clinical Pharmacology Reviewer, DCP 1, OCP
Sandra Suarez Sharp, Ph.D., Biopharmaceutics Reviewer, Office of New Drug Quality Assessment
Stephen Grant, M.D., Deputy Director, Division of Cardiovascular and Renal Products
Rajnikanth Madabushi, Ph.D., Clinical Pharmacology Team Lead, DCP 1, OCP
Brian Strongin, R.Ph., M.B.A., Chief Project Management Staff, DGIEP
CDR Stacy Barley, R.N., M.S.N., M.H.A., Senior Regulatory Project Manager, DGIEP

SPONSOR ATTENDEES
Tomas Bocanegra, M.D., Executive Vice President, Development
John Fort, M.D., Chief Medical Officer
Paul Ossi, Senior Vice President, Regulatory Affairs
Lisa Zimmerman, Vice President, Clinical Operations

Ying Zhang, Director, Biostatistics
Bruce Cao, Pharm.D., Director, Pharmaceutical Development
(b) (4) Consultant, Clinical Development
John Plachetka, Pharm. D., Chief Scientific Officer and CEO

1.0 BACKGROUND

POZEN wishes to gain agreement with the Division regarding certain aspects of the content and format of the proposed 505(b)2 New Drug Application (NDA) for PA32540 Tablets.

Pozen's description of the product: PA32540 Tablets contain 325 mg delayed-release aspirin in the core and 40 mg immediate- release omeprazole in the film coat. The omeprazole is immediately released and the release of the aspirin core is delayed (b) (4) PA32540 Tablets are for oral administration on a once daily regimen.

According to Pozen, the proposed indications for PA32540 Tablets are for patients who require 325 mg aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk for developing aspirin- associated gastric ulcers: (1) to reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) to reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, (3) to reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris, (4) in patients who have undergone revascularization procedures (CABG, PTCA) when there is a preexisting condition for which 325 mg aspirin is already indicated.

Additionally, Pozen indicates PA32540 is not recommended for acute treatment of cardiovascular or cerebrovascular events.

Ecotrin and Prilosec will serve as the Reference Listed Drugs for this 505(b)2 NDA.

The original NDA for PA32540 Tablets is scheduled for submission at mid-year 2012 and will include the clinical study report for the aspirin bioequivalence study discussed with the Agency in a teleconference on January 31, 2012.

2. DISCUSSION

Questions from POZEN are in plain text. The preliminary FDA responses sent to POZEN on April 19, 2012, are in **bold text**. The meeting discussion from April 23, 2012, is in ***bold italics***.

QUESTIONS AND RESPONSES

1. POZEN proposes to submit the NDA for PA32540 Tablets electronically in Electronic Common Technical Document (eCTD) format in accordance with the June 2008 Revision 2 ("Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications"). Are there any specific Division requirements in this regard?

FDA Response:
Yes we agree. Please refer to the eCTD website, located at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

Additional Discussion:
No additional discussion occurred. Pozen agrees with the FDA response as stated above.

2. POZEN intends to follow the April 2005 "Guidance for Industry Providing Regulatory Submissions in Electronic Format — Content of Labeling" for providing draft labeling in SPL format." Are there any specific Division requirements beyond the standard proposals in the guidance that POZEN should be aware?

FDA Response:
There are no specific Division requirements regarding the submission of the label, therefore please follow the April 2005 "Guidance for Industry Providing Regulatory Submissions in Electronic Format — Content of Labeling" for providing draft labeling in SPL format" guideline. Also ensure a word document version of the label is provided at the time of submission.

Additional Discussion:
No additional discussion occurred. Pozen agrees with the FDA response as stated above.

3. a) POZEN has partnered with (b) (4) to prepare and submit the final document to FDA. As this NDA will be POZEN's second eCTD application to this Division (see VIMOVO™ NDA 22-511), it is our understanding that POZEN will not be required to submit a sample eCTD prior to submission of the actual NDA application. Does the Agency agree?

FDA Response:
Yes we agree.
(Additionally)

- **Avoid using special characters except hyphens and underscores in file names Refer to Page 5 of PDF Specifications, located at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf**

- **Please make sure that the stf title in the stf.xml file and the leaf title of the stf referenced in the index.xml file match, to avoid validation error. Refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf**

- **To avoid validation errors, make sure all modified leaves are validated before submitting**

Additional Discussion:
No additional discussion occurred. Pozen agrees with the FDA response as stated above.

b) POZEN proposes to submit the original NDA for PA32540 Tablets in eCTD format on DVD. Subsequent sequences will be planned for submission using the Electronic Submissions Gateway (ESG). Does the Agency agree with this approach?

FDA Response:
Yes, we agree. We also recommend that you provide a paper copy of the cover letter and form, just in case the media proves unreadable.

Additional Discussion:
No additional discussion occurred. Pozen agrees with the FDA response as stated above.

4. POZEN plans to provide electronic SAS transport files (.xpt) with definition tables including raw data files and analysis data files for the clinical studies provided in the NDA. Does the Agency concur?

FDA Response:
Yes, we agree. Please review the Study Data Specifications document for additional information on content and structure of datasets and folders. Also, please note that every study data folder containing electronic datasets should contain a definition table. If datasets will be in standardized format (CDISC/SDTM or CDISC/ADaM), please note this in the definition table and in the reviewer's guide.

Additional Discussion:
No additional discussion occurred. Pozen agrees with the FDA response as stated above.

5. The ISE for this NDA will include two adequate and well controlled pivotal studies (studies PA32540-301 and PA32540-302) evaluating the incidence of gastric ulcers in cardiovascular disease patients in need of chronic aspirin therapy (325 mg) and who are at risk of developing aspirin-induced ulcers. Results of the primary (gastric ulcers) and secondary endpoints will be presented side by side for the two studies to demonstrate the consistent clinical benefit. In addition, all primary and secondary endpoints will be analyzed and summarized using pooled data from these two studies. The primary endpoint will also be summarized by demographics and risk factors for ulcer. Does the Agency agree with this general approach?

FDA Response:
Yes, we agree with the general approach.

Additional Discussion:
No additional discussion occurred. Pozen agrees with the FDA response as stated above.

6. The ISS for the NDA will include all patients and healthy volunteers treated in the clinical development program. The ISS will be focused on the overall treatment emergent adverse events, deaths, serious AEs, AEs leading to study discontinuation, laboratory results and vital signs. In addition, treatment emergent adverse events will also be summarized by demographics, risk factors, comorbidities and concomitant medications and drug exposure. All adverse events are coded with MedDRA 12.1. Does the Agency agree with this general plan?

FDA Response:

Please clarify how you intend to present cardiovascular safety data, including major adverse cardiovascular events (i.e., MACE or death, non-fatal MI and non-fatal stroke). Please also clarify how adjudicated vs. non-adjudicated MACE events will be presented.

You will also need to perform analyses to evaluate for a possible treatment interaction between omeprazole and clopidogrel with respect to MACE and gastrointestinal bleeding.

Additional Discussion:

Pozen stated that cardiovascular safety data including MACE will be presented as adjudicated and non-adjudicated data. The non-adjudicated cardiovascular data will be presented as outlined in the SAP for the ISS. Adjudication of CV events was conducted using independent, blinded experts and will also be presented in the ISS as a separate section. Experts consisted of cardiologists with experience in adjudication of CV events. The adjudication committee developed and approved a Charter that included the definition of events. All SAEs with cardiovascular preferred terms were reviewed and adjudicated. In addition, the Chair reviewed other non-SAE CV adverse events to determine if they required adjudication.

The FDA stated that the 2011 ACCF/AHA clinical practice guidelines for secondary prevention recommend a lower dose of aspirin than 325mg in patients with established coronary artery disease.

Pozen stated they could study the 81mg dose of aspirin however the omeprazole dose within the combination product would remain at 40mg. Their rationale was that the immediate release form of the omeprazole 40mg component of their product produces less acid suppression than the 40mg delayed release omeprazole in Prilosec (nearly 50% lower).

Pozen stated that meta-analyses indicate that GI bleeding rates are the same for 81mg and 325mg aspirin. The FDA stated they are interested in differences in rate of development of gastric ulcers for purposes of efficacy related to the omeprazole component. Pozen was asked if they have gastric ulcer incidence data comparing 81mg vs. 325mg aspirin. Pozen responded no.

FDA reminded Pozen that although the monograph has not changed, current clinical practice guidelines (based on evolving evidence) for dosing of aspirin for secondary prevention differ from the monograph. Additionally, the monograph indicates a range of doses (generally 75-325 mg daily) for all vascular indications except after coronary artery bypass grafting.

Presumably, patients with gastric ulcers and or at high risk for gastric ulcers should be given the lowest effective dose of aspirin. If the NDA is submitted, the product would likely be presented at an AC for input on approvability and labeling. The Division of Cardiovascular and Renal Products (DCRP) emphasized the importance of having an 81mg aspirin dose at the time of marketing approval. Pozen stated they have developed an 81mg combination product but have not conducted a full clinical efficacy trial with the product. They proposed submitting the CMC data and Phase I PK/PD for the 81mg product in the NDA to support its approval. The FDA stated they could not agree that these data would be adequate to support the 81mg product approval but would be willing to review it. Additional clinical studies may be needed. It will important to consider whether the addition of a PPI to 81mg ASA is necessary to reduce ulcers and whether potential risks from the addition of chronic use of a PPI is justified.

Pozen will take into account the current clinical practice guidelines and submit their data for the fixed dose combination of 81mg aspirin and 40mg omperazole.

7. PA32540 Tablets will be labeled for use in adults 18 years of age or older. POZEN intends to request a waiver from the requirements to perform pediatric studies and will provide justification at the time of submission of the original NDA. Does the Agency agree with this approach?

FDA Response:
Your approach appears reasonable.

Additional Discussion:
No additional discussion occurred. Pozen agrees with the FDA response as stated above.

8. POZEN proposes that a REMS is not required for PA32540 Tablets, which contains two well known actives with well-established safety profiles. POZEN proposes (b) (4) Does the Agency agree?

FDA Response:
We will determine if the product will require a Risk Evaluation and Mitigation Strategy (REMS) during the review. Please note (b) (4) Please note the labeled warning and precaution for administering high dose aspirin with Ticagrelor and the existence of a REMS. Your label must address safety issues related with aspirin that have been identified with the concomitant use of other drugs, in addition to other appropriate information regarding the aspirin component of your product.

Additional Discussion:
Pozen states they plan to include the statement, "Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor (b) (4)", in draft labeling.

FDA stated that wording similar to the proposed language will be discussed during labeling.

9. Does the Agency have any additional recommendations or requirements that the Sponsor should be aware of regarding the preparation of the eCTD NDA for PA32540 Tablets?

FDA Response:
No.

Additional Discussion:
No additional discussion occurred. Pozen agrees with the FDA response as stated above.

Additional Comments:
In light of the dose dependent safety issues associated with aspirin and proton pump inhibitors (PPIs), we believe the most appropriate indication for the proposed product, which contains 325mg ASA and 40mg omeprazole, is post CABG (b) (4)

Additional Discussion:
The FDA notified Pozen that this will be a review issue.

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Pozen requests to hold another teleconference with the Clinical Pharmacology team. The FDA informed Pozen that they would need to submit the meeting request.

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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/s/

STACY R BARLEY
04/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 78,747

MEETING MINUTES

POZEN INC.
Attention: Paul A. Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PA32540 (aspirin/omeprazole) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 31, 2012. The purpose of the meeting was to discuss your NDA program development which you consider to be stalled.

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

If you have any questions, call me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	Other
Meeting Date and Time:	January 31, 2012 from 3:00 p.m. – 4:00 p.m. EDT
Meeting Location:	Teleconference 877-407-0669; Passcode 37051763
Application Number:	IND 78,747
Product Name:	PA32540 (aspirin/omeprazole) Tablets
Indication:	**Secondary prevention of cardio- and cerebrovascular events and to reduce the incidence of gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers.**
Sponsor/Applicant Name:	Pozen
Meeting Chair:	Sue-Chih Lee, Ph.D.
Meeting Recorder:	Stacy Barley, R.N., M.S.N., M.H.A.

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products
Robert Fiorentino, M.D., M.P.H., Clinical Team Lead, DGIEP
Sue-Chih Lee, Ph.D, Clinical Pharmacology Team Lead, Division of Clinical Pharmacology (DCP) 3, Office of Clinical Pharmacology (OCP)
Insook Kim, Ph.D., Clinical Pharmacology Reviewer, OCP
Stephen Grant, M.D., Deputy Director, Division of Cardiovascular and Renal Products
Rajnikanth Madabushi, Ph.D., Clinical Pharmacology Team Lead, DCP 1, OCP
CDR Stacy Barley, R.N., M.S.N., M.H.A., Senior Regulatory Project Manager (DGIEP)

SPONSOR ATTENDEES

John Plachetka, Pharm.D., CEO and Chief Scientific Officer
Tomas Bocanegra, M.D., Executive Vice President, Development
John Fort, M.D., Chief Medical Officer
Paul Ossi, Senior Vice President, Regulatory Affairs
Lisa Zimmerman, Vice President, Clinical Operations
Ying Zhang, Director, Biostatistics
Bruce Cao, Pharm.D., Director, Pharmaceutical Development
(b) (4) Consultant, Pharmacokinetics
(b) (4) Consultant, Clinical Development
(b) (4) Consultant, Clinical Pharmacology

1.0 BACKGROUND

During POZEN's initial discussions on PA32540 Tablets in 2008, the FDA agreed that using salicylic acid was acceptable to demonstrate bioequivalence to the reference listed drug Ecotrin®. Study PA32540-104 was conducted, which demonstrated bioequivalence of PA32540 and Ecotrin® for salicylic acid as stated by Pozen. POZEN also stated that although PA32540-104 was not designed to analyze acetylsalicylic acid for bioequivalence, acetylsalicylic acid data was collected in accord with the FDA's request. FDA also suggested for Pozen to compare PA32540 to Ecotrin® with respect to platelet aggregation to establish bioequivalence, which was completed in study PA32540-110. Upon request by FDA, these data were submitted in communications dated July 8, 2011 and November 9, 2011 and, in POZEN's view, support the conclusion that PA32540 has been shown to be bioequivalent to Ecotrin®.

FDA issued an Advice letter of December 12, 2011 stating, "Although the salicylate PK parameters of your product meet the bioequivalence criteria, the aspirin PK parameters do not. You must further justify how the observed results provide an acceptable bridge."

POZEN proposes that a valid bridge has been established and provided data in the briefing document that they claim supports that conclusion.

The purpose of the meeting is to address the FDA's December 12, 2011 Advice letter regarding the use of acetylsalicylic acid to determine bioequivalence of PA32540 Tablets with Ecotrin® (RLD).

The specific objective of the meeting was to gain feedback from the FDA on the results of POZEN's PK studies that POZEN believes demonstrates that PA32540 Tablets are bioequivalent to Ecotrin and would allow them to submit a fileable 505(b)2 NDA for PA32540 Tablets.

2. DISCUSSION

Questions from POZEN are in plain text. The preliminary FDA responses sent to POZEN the morning of January 31, 2012, are in **bold text**. The meeting discussion from January 31, 2012, is in ***bold italics***.

QUESTIONS AND RESPONSES:

1. Does the Agency agree that the information and additional data provided herein (see Briefing Information) are adequate to establish a finding of bioequivalence of PA32540 Tablets with Ecotrin (RLD)?

FDA Response:

No. Our preliminary review of your study indicates that bioequivalence (BE) was not demonstrated between PA32540 and Ecotrin 325 mg based on acetylsalicylic acid. We acknowledge that lower doses of aspirin are used for secondary prevention; however, you must address the patients for whom clinicians specifically prescribe the 325 mg dose and

why bioequivalence is not necessary in those patients. In particular, we are very concerned about the dose of aspirin for CABG and the initial dose for PTCA. As a general comment, we do not recommend that you pool the data from multiple studies to establish a bioequivalence.

We also remind you that the ex vivo platelet aggregation study results may not be supportive of comparability between PA32540 and Ecotrin because clinical significance of the ex-vivo platelet aggregation study has not been well established. Consequently, the Agency does not have criteria for assessment of comparability based on this PD marker. In addition, your study PA32540-110 was conducted with concomitant clopidogrel with PA32540 and Ecotrin 325 mg, which allowed confounding effect of clopidogrel on platelet aggregation making the study results less useful for any definitive conclusion for aspirin part.

We remind you that our previous recommendation was made under the assumption of infeasibility of measurement of plasma acetylsalicylic acid (ASA) level and estimation of pharmacokinetic (PK) parameters following administration of delayed release aspirin products. However, the PK data on ASA following administration of Ecotrin 325 mg in your three studies further supports that the plasma acetylsalicylic acid level is measurable and PK parameters can be reasonably estimated for ASA. As such, we believe that ASA should be the primary endpoint for PK-based BE assessment, while salicylic acid remains as a secondary endpoint.

Additional Discussion:
Pozen proposed to conduct the additional BE study with acetylsalicylic acid as a primary endpoint. However, Pozen stated that the additional BE study would potentially delay their NDA submission and request to submit the study report within 3 months of the NDA being filed. They request agreement from the FDA that the review clock would not be extended if the study report data is submitted within the first 90 days of the NDA being filed. The FDA responded that the NDA should be complete at the time of submission.

Pozen stated in regard to the design of the additional BE study, they wish to follow the design and statistical methods and interpretation of results described in the Haidar, 2007 paper which was provided in the briefing document. FDA recommended they follow the draft guidance on Progesterone:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf***. Pozen requests to submit the protocol synopsis for the FDA to review. FDA is in agreement and plans to review the synopsis within a week of receiving the submission.***

Pozen stated that, (b) (4) (b) (4) ***FDA responded, the plan would be acceptable.***

2. Does the Agency agree that the submission of these data in our 505(b)2 NDA will result in a fileable application with regard to the ASA vs. SA issue cited in your December 12, 2011 Advice letter?

FDA Response:

See the response to question 1. Although the issues discussed above would not result in a refuse to file, they will be significant review issues that could negatively impact the action decision or labeling. If the product is not bioequivalent to Ecotrin based on ASA, the product could not carry an indication for revascularization procedures (and would likely need to include qualification statements to ensure that prescribers do not inadvertently use the product for these indications. However, we can not determine at this time if restrictive labeling could address our concerns. We recommend that you conduct another BE study with regard to acetylsalicylic acid to overcome these issues.

Additional Discussion:

No additional discussion.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Protocol Synopsis	Sponsor	1/31/12
Review of Protocol synopsis	FDA	7 business days after receipt of submission

5.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

STACY R BARLEY
02/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 78,747

MEETING MINUTES

POZEN, INC
Attention: Paul Ossi
Sr. Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PA32540 (aspirin 325mg/omeprazole 40mg) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 30, 2011. The purpose of the meeting was to discuss a proposed outcomes study for alternate dosage strengths of PA (aspirin/omeprazole combination product) and to gain agreement on the development program for approval of the additional strengths.

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

If you have any questions, call me at (301) 796-0942.

Sincerely,

{See appended electronic signature page}

Frances Fahnbulleh, PharmD
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES ATTACHED

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 30, 2011
Meeting Location:	WO/22, Room #1419 Silver Spring MD 20993
Application Number:	IND 78,747
Product Name:	PA32540 (aspirin/omeprazole) Tablets
Indication:	For the secondary prevention of cardio and cerebrovascular events in patients at risk for developing aspirin associated gastric ulcers
Sponsor/Applicant Name:	POZEN, Inc.
Meeting Chair:	Robert Fiorentino, M.D. (Clinical Team Leader)
Meeting Recorder:	Frances Fahnbulleh, PharmD (Regulatory Health Project Manager)

FDA ATTENDEES

Division of Gastroenterology Products
Donna Griebel, M.D., Director
Andrew Mulberg, M.D., FAAP, CPI, Deputy Director
Joyce Korvick, M.D.M.P.H., Deputy Director of Safety
Robert Fiorentino, M.D., M.P.H., Medical Team Leader
He, Ruyi, M.D.., Medical Team Leader
Anil Nayyar, M.D., Medical Team Leader
Sushanta Chakder, Ph.D., Pharmacology Supervisor
Maria Walsh, RN, MS, Assoc. Director for Regulatory Affairs, Office of Drug Evaluation III
Giuseppe Randazzo, Regulatory Scientist, Office of Drug Evaluation III
Frances Fahnbulleh, Pharm.D, Regulatory Project Manager
Brian Strongin, MBA, Chief Project Management Staff

Office of Clinical Pharmacology
Sue-Chih Lee, Ph.D., Team Leader
Insook Kim, Ph.D., Reviewer

Division of Biometrics
Mike Welch, Ph.D, Biometrics Supervisor
Freda Cooner, Statistical Reviewer

Division of Cardiovascular and Renal Products
Stephen Grant, M.D., Deputy Director

SPONSOR ATTENDEES

John Fort, M.D.	Chief Medical Officer
Paul Ossi	Senior Vice President, Regulatory Affairs
Lisa Zimmerman	Vice President, Clinical Operations
Ying Zhang	Director, Biostatistics
Bruce Cao, Pharm.D.	Associate Director, Pharmaceutical Development
(b) (4)	(b) (4) (consultant)
(b) (4)	(b) (4) (pK consultant)

1.0 BACKGROUND

IND 78,747 was submitted December 19, 2007 by Pozen, Inc. to investigate the use of PA32540 (aspirin/omeprazole) Tablets for the reduction in the occurrence of aspirin-related gastrointestinal ulcers for patients who require daily use of aspirin and are at risk of developing aspirin-associated ulcers. Pozen submitted a Special Clinical Protocol Assessment on June 4, 2008 for protocol PA32540-301, "A 6-Month Phase 3, Randomized, Double-Blind, Controlled, Parallel-Group, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Delayed Release Aspirin 325mg in Subjects Who Are at Risk for Developing Aspirin-Associated Ulcers". The Division's response was dated July 29, 2008.

MEETING OBJECTIVES

The purpose of this meeting is to discuss a proposal (b) (4) of PA32540 (aspirin 325mg/omeprazole 40mg) Tablets (currently in Phase 3), and gain agreement on the development program (b) (4). The desired outcome of the meeting is to gain agreement with the Agency on the design and analysis of a pivotal study protocol (PA32540-301), that if replicated in a second identical study, would support a 505(b)(2) NDA for PA 32540.

2. DISCUSSION

QUESTION # 1 (Original NDA):

Attachment 1A includes the studies previously agreed with the Agency that will support approval of the Original NDA for PA32540 Tablets. (b) (4)

Does the Agency agree?

FDA Response to Q#1:

No, we do not agree (b) (4)

(b) (4)

We recommend that efficacy and safety demonstrated in two well-controlled trials showing replication of the efficacy results for the proposed doses and indications in a well defined population. Evidence of efficacy based on a single trial should meet the criteria as defined in the efficacy guidance [Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf].

For the purposes of a 505(b)(2) bridging study, it appears acceptable to conduct a bioequivalence study between PA8140 and Ecotrin 81 mg. We reiterate that acetyl salicylic acid should be measured to demonstrate a bioequivalence.

Additional Comments

We also note that the current protocol under SPA (Study PA32540-104) does not appear to exclude concomitant use of clopidogrel, however the omeprazole label has been updated to avoid concomitant use of clopidogrel and omeprazole. You will need to revise the protocol (as well as the Investigator's Brochure and Informed Consent) to reflect this information. Please also provide information on the number of subjects receiving concomitant clopidogrel in the ongoing trial. You will need to revise the eligibility criteria and discuss how subjects already on clopidogrel will be discontinued from treatment.

In addition to safety concerns, concomitant use of omeprazole and clopidogrel will affect the interpretation of the study results. The current PLAVIX label states "Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of Plavix." Some of the decrease in GI bleeds observed in your proposed trial may be due to reduction of the anti-platelet effects of clopidogrel by omeprazole.

Further, the Informed Consent in the ongoing study should be revised to reflect the safety information related to bone risks described in PPI labels.

Discussion:
Safety concerns regarding concomitant use of clopidogrel and omeprazole were discussed. The sponsor stated that these issues were known before starting the trials and the Investigators in the ongoing trials were informed of the FDA warnings. The sponsor stated that the patients have been informed and consented regarding the potential interaction between Plavix and omeprazole.

Sponsor requested confirmation that the Studies 301 and 302 would be adequate to support filing an NDA, in light of previous SPA agreement.

FDA reiterated concerns about the need to establish a lowest effective dose for the PPI in light of recent safety labeling described above. The sponsor stated that they would present additional information to support the adequacy of filing with the 40mg omeprazole dose (b) (4)

Additional Discussion (not captured at meeting):

Although the studies intended to provide PK data on the combination of clopidogrel and lower doses of omeprazole are not available, based on the presentation of the sponsor, FDA agreed that the ongoing studies could continue to enroll patients receiving clopidogrel in the trials. However, FDA stated that interim safety information should be evaluated in the ongoing studies by the DSMB and the safety data should be submitted to the Agency before starting the new studies.

Post Meeting FDA Comments

FDA believes that aspirin BE should be demonstrated using serum aspirin (acetylsalicylic acid) levels rather than salicylate (salicylic acid), an inactive metabolite. A BE study measuring aspirin has been our recommendation for aspirin in the case of immediate-release products. However, it is not yet clear to us if there are potential issues with delayed release formulations that would make it difficult to establish BE based on the parent compound data. You stated in the meeting that aspirin plasma concentrations were measured in your BE study. In order to facilitate our future discussions on this matter, we request that you submit those data for our evaluation.

QUESTION # 2 (b) (4):

(b) (4)

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3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Investigator's Brochure	Sponsor	Submitted
Patient Informed Consent	Sponsor	Pending
Nov. 2009 letter to Investigators regarding interaction with clopidegrel	Sponsor	Submitted

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

FRANCES G FAHNBULLEH
05/25/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 78,747

Pozen, Inc.
Attention: Paul Ossi
Senior Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, North Carolina 27517

Dear Mr. Ossi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PA 32540 (aspirin/omeprazole).

We also refer to the meeting between representatives of your firm and the FDA on October 2, 2008. The purpose of the meeting was to discuss the Division's comments and recommendations included in the July 29, 2008 Special Clinical Protocol Assessment letter.

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

If you have any questions, call me at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 2, 2008
TIME: 9:00 AM
LOCATION: White Oak Building #22, Conference Room 1311
APPLICATION: IND 78,747
DRUG NAME: PA 32540 (aspirin/omeprazole)
TYPE OF MEETING: Type A; Post-Special Clinical Protocol Assessment Meeting

MEETING CHAIR: Hugo Gallo-Torres, M.D., Ph.D.

MEETING RECORDER: Brian Strongin, R.Ph., M.B.A.

FDA ATTENDEES: (Title and Office/Division)

NAME	OFFICE/DIVISION	TITLE
Donna Griebel, M.D.	Division of Gastroenterology Products	Director
Anne Pariser, M.D.	Division of Gastroenterology Products	Acting Deputy Director
Robert Temple, M.D.	Office of Medical Policy	Director
Hugo Gallo-Torres, M.D., Ph. D.	Division of Gastroenterology Products	Medical Team Leader
Wen-Yi Gao, M.D., Ph.D.	Division of Gastroenterology Products	Medical Officer
Mike Welch, Ph.D.	Division of Biometrics II	Statistical Team Leader
Sonia Castillo, Ph.D.	Division of Biometrics II	Statistical Reviewer
Sue Chih Lee, Ph.D.	Division of Clinical Pharmacology and Biopharmaceutics II	Clinical Pharmacology and Biopharmaceutics II
Brian Strongin, R.Ph., M.B.A.	Division of Gastroenterology Products	Chief, Project Management Staff

EXTERNAL CONSTITUENT ATTENDEES:

NAME	TITLE	COMPANY
Marshall Reese, Ph.D.	Executive Vice President, Product Development	Pozen, Inc.
John Fort, M.D.	Vice President, Chief Medical Officer	Pozen, Inc.
Paul Ossi	Senior Vice President, Regulatory Affairs	Pozen, Inc.
Eric Orlemans, Ph. D.	Senior Vice President, Clinical Development	Pozen, Inc.
Timothy Ressler, MS	Vice President, Regulatory Affairs	Pozen, Inc.
(b) (4)		Consultant

BACKGROUND:

IND 78,747 was submitted December 19, 2007 by Pozen, Inc. to investigate the use of PA32540 (aspirin/omeprazole) Tablets for the reduction in the occurrence of aspirin-related gastrointestinal ulcers for patients who require daily use of aspirin and are at risk of developing aspirin-associated ulcers. Pozen submitted a Special Clinical Protocol Assessment June 4, 2008 for protocol PA32540-301, "A 6-Month Phase 3, Randomized, Double-Blind, Controlled, Parallel-Group, Multi-Center Study to Evaluate the Incidence of Gastric Ulcers Following Administration of Either PA32540 or Delayed-Release Aspirin 325mg in Subjects Who Are at Risk for Developing Aspirin-Associated Ulcers". The Division's response was dated July 29, 2008.

MEETING OBJECTIVES:

The objective of this meeting is to address comments and resolve questions raised in the Agency's July 29, 2008 SPA (special protocol assessment) response letter. The desired outcome of the meeting is to gain agreement with the Agency on the design and analysis of a pivotal study protocol (PA32540-301), that if replicated in a second identical study, would support a 505(b)(2) NDA for PS 32540.

DISCUSSION POINTS:

Question 1a (Type A meeting):
Does the Agency agree with our proposed additional Inclusion Criteria as described above?

FDA response: Yes. We agree with the proposal of only enroll subjects who have been on aspirin 325 mg for the secondary prevention for at least three months.

Question 1b (Type A meeting):
Does the Agency agree with our proposed modification to Inclusion Criteria #1 as stated above?

FDA response: Yes. The proposed modification to Inclusion Criterion #1 as stated above is acceptable.

Question 1c (Type A meeting):
Does the Agency agree with the primary endpoint of endoscopic gastric ulcers?

FDA response: We reiterate our answer from the July 29, 2008 SPA-response letter. Further internal discussion of this issue is required.

(Discussion: The Division stated that the Agency has taken inconsistent approaches to the type of study needed to support Pozen's proposed claim. A Regulatory Briefing has been scheduled for early 2009 to discuss this issue and an Advisory Committee meeting is possible if the issue isn't resolved by the Regulatory Briefing. The goal is to achieve consistency if possible. Until then, the Division can not provide a definitive answer.

The sponsor responded that the feasibility of outcomes trials is an issue due to the low incidence of adverse gastrointestinal outcomes, approximately 1/2 %, while the meaningfulness of endoscopic trials is also an issue. Studies have investigated a correlation between endoscopic and outcomes trials. An endoscopic ulcer is a point on a continuum to an adverse clinical outcome. Pozen believes that endoscopic ulcers are predictive of adverse clinical outcomes.

The Division suggested that Pozen submit an argument supporting the use of endoscopic endpoints as a surrogate endpoint for adverse gastrointestinal clinical outcomes. Pozen could consider proposing accelerated approval.

The Division added that Pozen may begin their study at their own risk until this issue is resolved and that a clinical hold probably will not be placed on it. It may be possible to change endpoints if the blind has not been broken and more patients may be enrolled if necessary.

In response to the sponsor's question, the Division stated that similar advice will be given to other sponsors.)

Question 1d (Type A meeting):
If the Agency agrees that the primary endpoint in 1c above is the current acceptable endpoint for the PA studies under this SPA, does the Agency agree to remove the second paragraph in the response to question # 1 to avoid confusion?

FDA response: See response to Question 1(c).

Question 2 (Type A meeting):
Does the Agency agree with this primary endpoint as stated above?

FDA response: See the response to Question 1 (c).

Question 3 (Type A meeting):
Does the Agency agree with the proposed three-way stratification?

FDA response: The three-way stratification (non-specific NSAID users, celecoxib users, and subjects not currently on NSAIDs or celecoxib) appears to be acceptable.

Question 4a (Type A meeting):
Does the Agency agree that aspirin 325 mg is an appropriate and clinically relevant dose in the population to be studied?

FDA response: We agree that aspirin 325 mg is an appropriate and clinically relevant dose in the population to be studied.

Question 4b (Type A meeting):
Does the Agency agree that this modification will result in a homogenous population?

FDA response: The proposed enrollment is acceptable: 1) subjects with at least 3 months aspirin 325 mg use and 2) subjects who have undergone coronary revascularization or carotid endarterectomy at least 6 months prior to enrollment and for whom aspirin 325 mg is the appropriate dose.

Question 5a (Type A meeting):
We believe that salicylate levels have been used and continue to be appropriate for the determination of bioequivalence for aspirin products. Does the Agency agree?

FDA response*:* Due to the very short half-life of aspirin, we agree that bioequivalence may be established based on the salicylate PK data. However, since aspirin is the active component, we recommend that you also determine aspirin concentrations to obtain an estimate of comparative systemic exposure of aspirin.

Question 5b-1 (Type A meeting):
Does the Agency agree with this enrollment strategy?

FDA response: We agree that subjects who have acutely undergone surgical procedures prior to enrollment should not be included. However, the choice of aspirin dose should be based on accepted standards of care depending on the underlying condition of the patient and only patients requiring 325 mg of aspirin per day should be randomized into the trial.

Question 5b-2 (Type A meeting):
Does the Agency agree with the proposed modification to the indication and the inclusion of these subjects in the study?

FDA response: Please see the responses to Questions 5b-1 and 4b.

SPONSOR COMMENTS ON FDA's RESPONSE TO QUESTION # 6

In powering the study, the gastric ulcer rates (13% for aspirin 325 mg alone and 5% for aspirin plus PPI) were estimated from data in the following publications:

Laine L et al. (2004) Gastroenterol **127**:395-402.
Goldstein JL et al. (2006) Aliment Pharmacol Ther **23**:1489-98.
Goldstein JL et al. (2007) Clin Gastroenterol Hepatol **5**:1167-1174.
Cryer B. (2005) Am J Gastroenterol **100**:S59.

Copies of publications are attached for convenience (see Appendix 4).

FDA Response: If your effect size and aspirin-alone ulcer rate is correctly specified, then the study is adequately powered.

Question 6-1 (Type A meeting):
Does the Agency agree (b) (4) *?*

FDA Response:

No. (b) (4)

(b) (4)

Question 6-2 (Type A meeting):
As requested, (b) (4) *. Does the Agency agree?*

FDA Response: No. We do not agree (b) (4) **.**

Question 6-3 (Type A meeting):
As requested, (b) (4) *Does the Agency agree?*

FDA Response: No. We do not agree (b) (4)

Question 6-4 (Type A meeting):
Does the Agency agree?

FDA Response: If indeed, the second protocol is identical to the protocol that has been reviewed as an SPA, submission of the second protocol as an SPA is not necessary. Otherwise it should be submitted as a SPA.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

Pozen may submit an argument supporting the use of endoscopic endpoints as a surrogate endpoint for adverse gastrointestinal clinical outcomes.

ATTACHMENTS/HANDOUTS:

None

IND 78,747 Type A Minutes Ltr.doc

Linked Applications	Sponsor Name	Drug Name
IND 78747	POZEN	PA32540

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

/s/

BRIAN K STRONGIN
10/24/2008