CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-281

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-281

NAME OF APPLICANT / NDA HOLDER
Schering-Plough HealthCare Products, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zegerid® OTC Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
Omeprazole Sodium Bicarbonate	Omeprazole 20 mg Sodium Bicarbonate 1100 mg

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,489,346 B1	December 3, 2002	July 15, 2016

d. Name of Patent Owner	Address *(of Patent Owner)*	
The Curators of the University of Missouri	615 Locust Street, Building 304F	
	City/State: Columbia, MO	
	ZIP Code: 65211	FAX Number *(if available)*: (573) 882-1130
	Telephone Number: (573) 882-2821	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Schering-Plough HealthCare Products, Inc., the applicant has a place of business in the U.S.	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Claim Number (*as listed in the patent*): 24, 26, 31, 32, 34, 35, 37, 49, 50, 51, 55, 56, 91, 92 and 93 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*

See Attachment 1.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	3/3/08

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Henry Hadad	
Address SCHERING CORPORATION, Patent Dept., K-6-1-1990 2000 Galloping Hill Road	City/State Kenilworth, New Jersey
ZIP Code 07033-0530	Telephone Number (908) 298-2906
FAX Number *(if available)* (908) 298-5388	E-Mail Address *(if available)* henry.hadad@spcorp.com

Form FDA 3542a
ZEGERID® OTC Capsules
NDA No. 22-281
USPN 6,489,346 B1

ATTACHMENT 1

Item 4.2a

USE

- treats frequent heartburn (occurs ***2 or more*** days a week)
- not intended for immediate relief of heartburn, this drug may take 1 to 4 days for full effect

Directions

- adults 18 years of age and older
- this product is to be used once a day (every 24 hours), every day for 14 days
- it may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours

14-Day Course of Treatment

- swallow 1 capsule with a glass of water before eating in the morning
- take every day for 14 days
- do not take more than 1 capsule a day
- do not chew or crush the capsule
- do not open capsule and sprinkle on food
- do not use for more than 14 days unless directed by your doctor

Repeated 14-Day Courses (if needed)

- you may repeat a 14-day course every 4 months
- **do not take for more than 14 days or more often than every 4 months unless directed by a doctor**

- children under 18 years of age: ask a doctor

Paragraph IV Certification

Pursuant to §505(b)(2) of the Federal Food, Drug and Cosmetic Act and the Food Drug Administration regulations codified in 21 CFR §314.50(i)(1)(i)(A)(4), Schering-Plough HealthCare Products, Inc. herby certifies with respect to each of United States Patent Numbers 4,786,505, 4,853,230, 5,690,960, 5,753,265, 5,817,338, 5,900,424, 6,403,616, 6,428,810 that such patents are invalid or will not be infringed by the manufacture, use or sale of Zegerid OTC™ Omeprazole/Sodium Bicarbonate Capsules, for which the §505(b)(2) application is being submitted.

Pursuant to 21 CFR §314.50(i)(1)(i)(A)(4), Schering-Plough Healthcare Products, Inc. certifies that the owners of United States Patent Numbers 4,786,505, 4,853,230, 5,690,960, 5,753,265, 5,817,338, 5,900,424, 6,403,616, 6,428,810 and the holder of the approved New Drug Application 21-229 will be sent notification of non-infringement and/or invalidity of the above-referenced patents as required by 21 CFR §314.52(a) that contains the information described in 21 §CFR 314.52(c).

Henry Hadad
Vice President, Assoc. General Counsel

March 10, 2008
Date

EXCLUSIVITY SUMMARY

NDA # 22-281 SUPPL # HFD #

Trade Name Zegerid OTC

Generic Name 20 mg omeprazole & 1100 mg sodium bicarbonate

Applicant Name Schering-Plough Healthcare Products, Inc

Approval Date, If Known 12/08/09

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.

PK study to compare Zegerid OTC(omeprazole & sodium) to Prilosec OTC (omeprazole magnesium)

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?

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?

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).

NDA# 21-849	Omeprazole 20mg & 40mg with sodium bicarbonate 1.1 GM capsule
NDA# 21-636	Omeprazole 20mg & 40mg with sodium bicarbonate 1.68 GM packet for oral suspension
NDA# 21-850	Omeprazole 20mg & 40mg with sodium bicarbonate 600 mg and magnesium hudroxide 700mh chewable tablet

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:

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:

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"):

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 # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # 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: Mary R. Vienna
Title: Regulatory Project Manager
Date: 11/12/09

Name of Office/Division Director signing form: Joel Schiffenbauer
Title: Deputy Director, DNCE

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Schering-Plough HealthCare Products, Inc., is not claiming any marketing exclusivity under the provisions of 21 CFR §314.108.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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

/s/

MARY RUSSELL R VIENNA
11/30/2009

JOEL SCHIFFENBAUER
11/30/2009

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-281 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DNCE PDUFA Goal Date: 01-10-09 Stamp Date: 03-10-08

Proprietary Name: Zegerid OTC

Established/Generic Name: Omeprazole 20mg and Sodium Bicarbonate 1100 mg

Dosage Form: capsule

Applicant/Sponsor: Schering-Plough

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treats frequent heartburn (occurs 2 or more days per week).

Q1: Is this application in response to a PREA PMC/PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC/PMR #:_____

Does the division agree that this is a complete response to the PMC/PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

☒ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☒ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification: It is clinically inappropriate for Zegerid to be available OTC for pediatric patients up to 18 years of age. Pediatric gastroenterologists recommend that children with symptoms of gastroesophageal reflux be examined by physicians for possible complications, and the treatment of frequent heartburn in the pediatric population should be under the direction of a physician. The OTC availability of Zegerid and other proton pump inhibitors (PPI) would be counter to this indication. Omeprazole is the only currently approved PPI for OTC use, and it is not approved for patients 17 years of age and younger.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

Mary R Vienna
12/8/2008 02:28:09 PM

Schering-Plough HealthCare Products 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.

04-MAR-2008

John O'Mullane, Ph.D.

Date

Group Vice President, Research and Development

Schering-Plough HealthCare Products, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

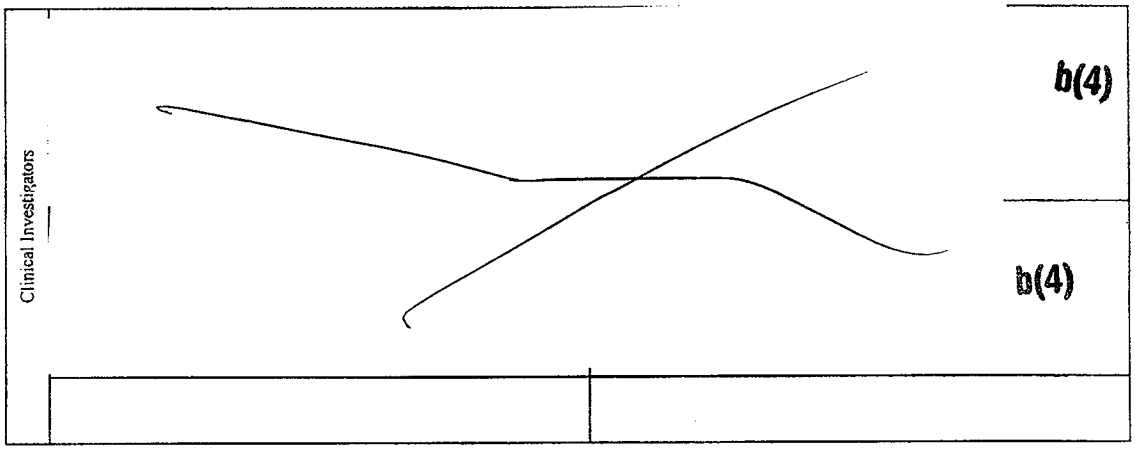
Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).



☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Luis M. Salmun, M.D.	Senior Director, Clinical Research and Medical Affairs
FIRM / ORGANIZATION: Schering-Plough HealthCare Products, Inc.	
SIGNATURE	DATE: 3/6/08

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-281	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Zegerid® OTC Established/Proper Name: Omeprazole and Sodium Bicarbonate Dosage Form: capsule Strengths: 20 mg/1100 mg		
Applicant: Schering-Plough Healthcare Products, Inc.		
Date of Receipt: 03-10-2008		
PDUFA Goal Date: 01-10-2009	Action Goal Date (if different): 01-09-2009	
Proposed Indication(s): Treats frequent heartburn		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☒

*If "**YES**," proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 21-229, Prilosec OTC™ 20 mg tablets	Pharmacokinetic data

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

   Pharmacokinetic studies to bridge proposed Zegerid capsule to Prilosec OTC (referenced drug)

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

   YES ☐ NO ☒

   *If "**NO**," proceed to question #6.*

   (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

   YES ☐ NO ☐

   *If "**NO**", proceed to question #6*

   *If "**YES**", list the listed drug(s) identified by name and answer question #5(c).*

   (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

   YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #11.*

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Prilosec OTC™ (omeprazole magnesium) 20 mg delayed release tablets	21-229	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

YES ☐ NO ☐

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

9. Were any of the listed drug(s) relied upon for this application:
   a. Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

   b. Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

   c. Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d.1.*
*If "**NO**", proceed to question #10.*

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The change from the listed drug: the application seeks the approval of omeprazole and sodium bicarbonate, rather than omeprazole magnesium; and provides for a change in dosage form from tablet to capsule.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☒ NO ☐

*If "**NO**," to (a) proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☒

*If "**YES**" and there are no additional pharmaceutical equivalents listed, proceed to question #13.*

*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): NDA 21-849 Zegerid (Omeprazole; sodium bicarbonate) 20 mg capsule

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

*If "**NO**", proceed to question #13.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☒

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #13.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): NDA 21-849 Zegerid (Omeprazole; sodium bicarbonate) 40 mg capsule; NDA 21-636 Zegerid (Omeprazole; sodium bicarbonate) 20 mg and 40mg powder for suspension.

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

    Listed drug/Patent number(s): 4786505, 4853230, 5690960, 5753265, 5817338, 5900424, 6403616, and 6428810

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

    YES ☒ NO ☐

    *If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

    Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? *(Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)*

    ☐ No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))

    ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

    ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

    Patent number(s):

    ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

    Patent number(s):

    ☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

    Patent number(s): 4786505, 4853230, 5690960, 5753265, 5817338, 5900424, 6403616, and 6428810

    If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

    YES ☒ NO ☐

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

Date Received: June 10, 2008

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES ☐ NO ☒

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):
If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES ☐ NO ☐

☐ Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

/s/

Mary R Vienna
1/6/2009 09:54:11 AM
CSO

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-281 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Zegerid OTC Established/Proper Name: Omperazole/Sodium Bicarbonate Dosage Form: Capsules		Applicant: Schering-Plough Healthcare, Inc. Agent for Applicant (if applicable):
RPM: Mary Vienna		Division: DNCE

NDAs: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): NDA 21-229; Prilosec OTC (omeprazole magnesium 20mg) Provide a brief explanation of how this product is different from the listed drug. NDA 22-281 active ingredients are omeprazole and sodium bicarbonate, dosage form is capsule NDA 21-229 active ingredient is omeprazole magnesium, dosage form is delayed release tablet ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☒ No changes ☐ Updated Date of check: 11-24-09 **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	12-08-09
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR 01-06-09

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

❖ Application Characteristics[2]	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☒ Rx-to-OTC partial switch ☐ Direct-to-OTC 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 Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	11-12-08
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ 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
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☒ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	12-01-09
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 12-01-09 CR 01-06-09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	10-22-09
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 10-28-09; 08-04-08 N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEDP ☐ DRISK ☐ DDMAC ☐ CSS ☒ Other reviews 11-03-09; 12-04-08; 11-25-08
Administrative/Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	❖ 505(b)(2) review: 01-06-08 ❖ RPR filing review: 08-20-08 ❖ DNCE clinical review: 05-06-08 ❖ DGP clinical review: 04-29-08 ❖ CMC review: 04-29-08 ❖ Clin/Pharm review: 05-06-08 ❖ Pharm/Tox review: 05-05-08 Labeling review: 04-17-08
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in 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
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date of mtg; approvals only)*	☐ Not applicable 11-12-08
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 10-30-07
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	PIND mtg 02-07-07; T-con mtg 04-15-07; Type A mtg 03-03-09
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11-30-09, 01-06-09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	DNCE: 10-30-09; 12-02-08
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None 09-08-08
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	located in clinical reviews: 10-30-09; 12-02-08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	12-02-08
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DGP: 12-10-08
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • 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
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11-06-09, 12-11-08, 11-10-08
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None 12-03-08
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11-26-08
❖ 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
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) *(indicate date for each review)*	☐ None 10-22-09, 01-06-09, 12-03-08
• ONDQA Biopharmaceutics review *(indicate date for each review)*	
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ 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)*	10-07-08
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 10-09-09 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	 Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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

/s/

MARY RUSSELL R VIENNA
12/01/2009

The sponsor was not on the AIP list during this application review.

Mary R. Vienna

Mary R. Vienna, Regulatory Project Manager

Date: 11/30/09

There are no Postmarketing Commitments for this application.

Mary R. Vienna, Regulatory Project Manager

Date: 11/30/09

No P/T consults were generated for this application.

Mary R. Vienna

Mary R. Vienna, Regulatory Project Manager

Date: 11/30/09

There was no DSI Audit for Clinical Studies performed for this application review.

Mary R. Vienna, Regulatory Project Manager

Date: 11/30/09

Refer to Clinical Review for Safety Update Reviews for Review Cycle 1 & Cycle 2.

Mary R. Vienna

Mary R. Vienna, Regulatory Project Manager

Date: 11/30/09

Refer to DARRTS record for incoming regulatory submissions.

Mary R. Vienna

Mary R. Vienna, Regulatory Project Manager

Date: 11/30/09

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-281

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Mr. Cochran:

We acknowledge receipt on June 8, 2009 of your June 6, 2009 resubmission to your new drug application for Zegerid™ OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules.

We consider this a complete, class 2 response to our January 6, 2009 action letter. Therefore, the user fee goal date is December 8, 2009.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

If you have any questions, call me at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Mary R. Vienna
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
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/

Mary R Vienna
6/18/2009 08:55:31 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-281
Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Mr. Cochran:

Please refer to your new drug application (NDA) dated March 10, 2008, received March 10, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid™ OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules.

We also refer to your March 25, 2009 submission, containing a proposal for the analyses of deaths and cases with serious outcomes from the AERS and WHO ex-US databases.

We have reviewed the referenced material and have the following comments and recommendations:

1. Your approach to postmarketing safety analysis is generally acceptable. We understand that you do not have ready access to the case report forms for deaths and serious adverse events, and therefore will provide analyses based on line-listing information. However, we request that AERS identification numbers (ISR numbers) of these cases should accompany line listings so that FDA can access the narratives to verify your interpretation of omeprazole involvement in any cases identified in your analyses.

2. You propose using actual unit sales based on marketing data for the relevant periods in order to obtain appropriate denominators for calculating rates of adverse event occurrence. However, for information on prescription use of omeprazole, we believe that actual units dispensed, rather than units sold, should be used. Please provide your rationale for whichever denominator you choose to use. You should also specify your sources of this proprietary marketing information.

3. Submit case report numbers (ISR numbers) for deaths and cases with serious adverse events involving the following settings:
    a. Omeprazole was the sole suspect drug
    b. Available re-challenge and de-challenge information
    c. Labeled adverse events vs. adverse events not already labeled

4. We remind you that your integrated analysis should include any publications (with copy of articles) resulting from controlled clinical trials in which 20 mg and 40 mg omeprazole doses were assessed concurrently.

If you have any questions, call Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
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/

Joel Schiffenbauer
4/2/2009 08:45:00 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-281

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Mr. Cochran:

Please refer to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid™ OTC (omeprazole 20mg & sodium bicarbonate 1100mg) capsules.

We also refer to the meeting between representatives of your firm and the FDA on March 3, 2009. The purpose of the meeting was to discuss FDA comments made in the Complete Response letter of January 6, 2009.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

NDA 22-281

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 3, 2009

TIME: 10:00 – 11:00 a.m. EST

LOCATION: White Oak CDER Office Building 22
Conference Room 1421
10903 New Hampshire Avenue
Silver Spring, MD 20993

APPLICATION: NDA 22-281

DRUG NAME: Zegerid OTC (omeprazole 20mg and sodium bicarbonate 1100mg) capsules

TYPE OF MEETING: Type A

MEETING CHAIR: Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation

MEETING RECORDER: Mary Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation

FDA ATTENDEES:

Division of Nonprescription Clinical Evaluation
Joel Schiffenbauer, M.D., Deputy Director
Lesley Furlong, M.D., Medical Team Leader
Christina Chang, M.D., M.P.H., Medical Officer
CAPT Laura Shay, R.N., M.S., C-ANP, Social Science Analyst
Murewa Oguntimein, M.H.S., C.H.E.S, Social Science Analyst
CAPT Mary Vienna, R.N., M.H.A., Regulatory Project Manager

Division of Nonprescription Regulation Development
Marina Chang, R.Ph., Interdisciplinary Scientist Team Leader
Reynold Tan, Ph.D., Interdisciplinary Scientist Reviewer

Division of Gastroenterology Products
Wen-Yi Gao, M.D., Medical Officer

Office of Clinical Pharmacology and Biopharmaceutics
Tien-Mien Chen, Ph.D., Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment
Christopher Hough, Ph.D., Chemistry Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Schering Plough HealthCare Products
John O'Mullane, Ph.D., Group Vice President, R&D
Stephenie Barba, Vice President, Regulatory Affairs
Paul Starkey, M.D., Senior Director, Medical Affairs
Bill Cochran, Senior Manager, Regulatory Affairs

Santarus, Inc.
E. David Ballard II, M.D., Senior Vice President, Clinical Research, Medical and Scientific Affairs
Warren Hall, Senior Vice President, Product Development and Manufacturing

Consultant

b(4)

1.0 BACKGROUND:

On March 10, 2008, Schering Plough Healthcare Products, Inc. (Schering) submitted a new drug application (NDA 22-281) for Zegerid OTC (omeprazole 20mg and sodium bicarbonate 1100mg) capsules. FDA issued a Complete Response action letter on January 6, 2009.

Schering submitted a meeting request to the FDA for a type A meeting on January 22, 2009 to discuss FDA comments made in the Complete Response letter.

In the meeting package submitted on February 17, 2009, Schering provided an overview of Zegerid PK data, additional safety data with proposed analyses, and proposed labeling for Schering's Complete Response.

2.0 MEETING OBJECTIVES:

To obtain FDA feedback and guidance on the data required to address the deficiencies identified in the January 9, 2009 Complete Response letter.

3.0 DISCUSSION:

Preliminary responses to the questions enclosed in the February 17, 2009 meeting package were sent to Schering via e-mail on March 2, 2009. These questions and preliminary FDA responses

are listed below in italics. A record of the discussion that occurred during the meeting is presented following the question and response to which the discussion pertained.

3.1 Question 1

Section 11.0 provides additional justification to support the scientific conclusion that the higher C_{max} seen with Zegerid OTC Capsules compared to Prilosec OTC Tablets (623 ng/mL compared to 362 ng/mL) is not expected to have any clinically meaningful impact on safety for the following reasons:

- Omeprazole has a unique pharmacology in so far as the activated pro-drug is generated in a highly selective acid-compartment of the parietal cell and in no other tissues of the body. It stands to reason that fleeting concentrations of non-reactive pro-drug are less relevant than total exposure of activated pro-drug over time. This argues that AUC is the most important parameter in estimating the consequences of drug exposure with respect to safety. Zegerid OTC Capsules and Prilosec OTC 20 mg Tablets are bioequivalent with respect to AUC and, therefore, would be expected have a similar safety profile. The rapid absorption of omeprazole observed after Zegerid OTC Capsule administration is entirely expected for this type of non-enterically coated formulation. The C_{max} for Zegerid OTC Capsules exceeds the C_{max} for Prilosec OTC Tablets for a very brief period of time (less than 2% of the time over a 24 hour period).

- The Agency has previously made a determination, as part of their review of Prilosec OTC Tablets, that they did not believe that a 60% increase in C_{max} (and a 100% increase in AUC) associated with the interaction of clarithromycin and omeprazole was of significant clinical concern.

- In reviewing the data from individual patients in the comparative bioavailability studies we began to get additional insights into what might be behind the observed differences in C_{max} values. You will see that whereas the calculated mean of the individual C_{max} values for Zegerid OTC Capsules is higher than that for the Prilosec OTC Tablet arm, this is more of a mathematical consequence of the impact of a low C_{max} cohort in the Prilosec OTC Tablet arm on the numerical average. This cohort makes it appear that the C_{max} value for Zegerid OTC Capsules is *increased* when in reality the C_{max} value for Prilosec OTC Tablets is *decreased* due to this averaging phenomena. Most striking was that only 5 of 169 subjects had a C_{max} value with Zegerid OTC Capsules that was higher than the highest Prilosec OTC Tablets C_{max} value and that the highest levels of C_{max} attained with Zegerid OTC Capsules do not differ greatly from the highest levels of C_{max} attained with Prilosec OTC Tablets.

Does the Agency agree that the higher C_{max} observed with Zegerid OTC Capsules compared to Prilosec OTC is not expected to have any clinically meaningful effect on safety?

FDA Preliminary Response

We do not agree. You have not provided adequate data to demonstrate that despite the higher Cmax, Zegerid 20 mg capsule is as safe as Prilosec OTC 20 mg tablet or that there is no clinically important difference in the safety profiles of prescription Prilosec 20 and 40 mg capsules. The information you have presented does not address whether the higher Cmax

contributes to the incidence of adverse events. We also have the following comments in response to the issues you raise in your question:

We are not aware of any data which demonstrate that the duration at Cmax relates to the safety profile of your drug.

We disagree with your conclusion that bioavailability of Zegerid is similar to that of Prilosec OTC and clarithromycin interaction. The Cmax of Zegerid 20 mg capsule results in an increase 2.2 times (ratio of geometric means) that of Prilosec OTC tablets; this is beyond the Cmax increase associated with clarithromycin. The temporary increase in Cmax exposure would only be in consumers taking clarithromycin concurrently, rather than all consumers; furthermore, having been prescribed an antibiotic, these individuals would be under the care of a healthcare provider.

We disagree with your conclusion that the discrepancy between the mean Cmax values of Zegerid 20 mg capsule and Prilosec OTC tablet resulted primarily from a cohort of low Cmax values in the Prilosec OTC treatment arm. According to figure 3 (page 20) of your briefing package, the scatter plot shows that the outliers occurred in the Zegerid 20 mg capsule treatment arm.

Also see our response to question 3 regarding additional safety analyses needed.

Additional Discussion for Question 1:
Schering discussed the pharmacology of omeprazole and reiterated their opinion that the brief duration during which the pro-drug remains in the gastric lumen and the brief time during which the Cmax for Zegerid exceeds that of Prilosec OTC, should not result in significant safety issues. Schering further expressed the opinion that the extent of clinical experience with omeprazole has supported their position that the higher Cmax does not result in clinically significant safety concerns. No new data were presented. FDA had no additional comments.

3.2 Question 2

Section 12.0 provides a comprehensive overview of all Zegerid PK data and systematically demonstrates that the mean C_{max} for Zegerid OTC Capsules always falls below the mean C_{max} for Prilosec 40 mg Rx. Nine Zegerid PK studies have been conducted over time and in no study does the mean C_{max} of Zegerid OTC Capsules exceed the mean C_{max} of Prilosec 40 mg. The consistency of the PK data obtained for Zegerid 20 mg, Prilosec 20 mg and Prilosec 40 mg in multiple studies over a period of time provides adequate support the cross study comparison included in the Zegerid OTC Capsules NDA. Furthermore, the pharmacokinetic data obtained in these nine studies is consistent with pharmacokinetic data obtained in an independent study published in 2005 that that included both omeprazole 20 and 40 mg.

Does the Agency agree that the data provided supports our conclusion that the mean C_{max} of Zegerid OTC Capsules has always been shown to be less than the mean C_{max} of Prilosec 40 mg Tablets?

FDA Preliminary Response

Based on the limited data presented in your briefing package, your approach of using historic data and cross study comparisons, in providing support for concluding that the mean Cmax of Zegerid 20 mg capsule has been lower than the mean Cmax of Prilosec 40 mg tablet, may be acceptable. However, you will need to provide additional data to support these cross study comparisons and to address a number of our concerns. For example, given the substantial inter-subject variation, both mean Cmax and standard deviation should be examined. In addition, you should provide information related to study designs, study populations, study conditions, administration conditions (related to timing of food), assay methods, inter-subject variation, and safety profile, in order to address concerns with cross study comparisons. A summary table of side-by-side comparison on these parameters should be provided.

Additional Discussion for Question 2:
The Agency agreed to consider appropriately pooled data. Schering stated that conditions, including use of the same laboratory, have been similar across PK studies. Schering committed to provide details from these PK studies, including a summary table, to support the argument that the Cmax of Zegerid 20 mg capsule is lower than Cmax of Prilosec 40 mg tablet. In addition, Schering is prepared to explain their rationale in pooling these studies, and to address any possible differences in study designs and when subjects were allowed to eat. Lastly, Schering agreed that the analysis will also include the pooled individual Cmax values across the studies to account for variability, rather than simply focusing on the mean Cmax values of each study.

3.3 Question 3

Section 13.0 of this briefing package provides additional data as well as proposed analyses that we intend to include in our Complete Response to show that Zegerid OTC Capsule has a safety profile that is comparable to Prilosec OTC Tablets and that Prilosec 40 mg and Prilosec 20 mg have comparable safety profiles. Please advise if you require additional analyses to support the safety of Zegerid OTC Capsules.

FDA Preliminary Response

The analyses presented in section 13 of your briefing package and the proposed analyses presented in section 15 are appropriate and will address our needs. However, in regards to the presentation of safety data, we have the following additional recommendations:

In addition to providing safety data summarized in tabular form, you should provide detailed analyses of deaths and cases with serious outcomes from AERS and WHO exUS databases. For example, there were 330 deaths in AERS and 33 deaths in WHO ex US involving omeprazole (from NDA 22-281 submission). For each case, you should provide an assessment of whether omeprazole was related to the deaths. Potential duplicate cases should be clearly identified and excluded from your analysis. This same process should be repeated for cases with serious outcomes. Besides the case report forms for the deaths and discontinuations that you will be submitting (as described under section 15), you should be prepared to provide case report forms for cases with serious outcomes, if requested.

You should also provide an analysis of the safety of Zegerid 20 mg compared to 20 mg and 40 mg omeprazole in controlled clinical trials. Safety data comparing Zegerid 20 mg with Zegerid 40 mg may also be helpful to support the safety of your 20 mg product, if there is no difference in the safety profiles of these doses. Where available, data either from controlled trials or from postmarketing safety databases, should be presented with appropriate denominators and numerators. For example, in Table 5 (on page 31) of your submission, the denominators for Prilosec OTC trials were number of patients in the trials. However, the denominators for Zegerid formulations were number of adverse events. This kind of comparison would not be meaningful unless the same denominators (i.e., number of patients) were used in calculating frequency of adverse events.

The ISS should include description, analysis and interpretation of the safety information from the studies you conducted, as well as from postmarketing safety databases for Zegerid/omeprazole products. Please analyze each safety database separately. For each database the analyses should include the following information:

- *Deaths*
- *Serious adverse events*
- *Common adverse events (e.g., > 1% in frequency)*
- *Laboratory findings, vital signs, physical examination*
- *Overdose experience*

Provide your own summary/conclusion and interpretation of the above information.

Only an update of medical literature review relevant to safety since the NDA submission would be needed.

Additional Discussion for Question 3:
FDA noted that the original NDA submission lacked an integrated assessment on data from controlled clinical studies, postmarketing data, and literature review. Schering committed to providing a global analysis on Zegerid and omeprazole in the Complete Response (CR). The CR submission will also include presentation of safety data on omeprazole as summarized in the briefing package for this meeting. In addition, presentation of data will utilize appropriate denominators to facilitate meaningful comparisons between different doses.

Schering then relayed the challenges in analyzing post-marketing safety data from AERS and WHO databases and requested additional guidance. In particular, Schering does not have ready access to postmarketing case reports that are not in their in-house database. FDA recommended that Schering submit a specific description of what data they have available, and its limitations, from postmarketing safety databases such as AERS, how they will present it in the Complete Response, before the application is filed, and FDA would provide feedback on such a proposal.

3.4 Question 4

Section 13.3 provides a detailed overview of the data we will submit to demonstrate that despite the higher C_{max} compared to Prilosec OTC Tablets, Zegerid OTC Capsules has an acceptable safety profile in the Asian population. These data include:

- The pharmacology of omeprazole indicates that AUC is the critical parameter when assessing drug exposure and safety. Since Zegerid OTC Capsules and Prilosec OTC Tablets are bioequivalent with respect to AUC, a comparable safety profile in Asians can be expected.
- The C_{max} for Zegerid OTC Capsules relative to the C_{max} for Prilosec OTC Tablets is not expected to be significantly increased in the Asian population. Increased plasma exposure in the Asian population is thought to be the result of slower metabolic rates compared to a non-Asian cohort. However, it is worth noting that even at the slower rate, the plasma half life of omeprazole is still less than 2 hours. The higher transient C_{max} values observed after Zegerid OTC Capsules administration compared to Prilosec is primarily attributed to rapid absorption; an expected observation with the Zegerid formulation. As there is no difference in the metabolic rates of Zegerid OTC Capsules and Prilosec OTC Tablets (as evidenced by the fact that they are bioequivalent with respect to AUC), it is not expected that the C_{max} in the Asian population after Zegerid OTC Capsules administration will be significantly different than the C_{max} in non-Asians.
- A review of the Santarus Adverse Event Database for Zegerid does not reveal any significant safety concerns in the Asian population.

Does the Agency agree that the proposed data is sufficient to support the safety of Zegerid OTC Capsules in the Asian population?

FDA Preliminary Response

No, we do not agree. You have not adequately addressed our concern regarding the risk/benefit assessment when Zegerid is used in this population. As we previously commented, with the use of Zegerid 20 mg capsule, many Asian consumers will exhibit both an increase in Cmax as well as AUC, effectively receiving a higher dose of omeprazole than Prilosec OTC 20 mg. To our knowledge there are no data demonstrating that doses higher than 20 mg of omeprazole provide any additional benefit for consumers with heartburn. Further, you have not provided a rationale as to why these consumers should be treated with a formulation that provides greater exposure without additional benefit.

The limited safety information you have provided for Asian subjects does not appear to adequately address the safety profile of omeprazole in this population. If you are unable to provide sufficient safety data in this population an alternative approach would be to include a statement in the label addressing this issue.

Additional Discussion for Question 4:
Schering requested clarification regarding FDA's safety concern for the Asian population, given that Zegerid and Prilosec OTC have comparable AUCs. FDA reiterated that the higher Cmax is specific to Zegerid formulation. The combination of the higher Cmax and a 4-fold increase in AUC associated with omeprazole (relative to Caucasian population) results in a greater overall exposure in the Asian population. In the absence of data to show that 40 mg omeprazole is more effective than 20mg for the treatment of heartburn, this population would receive a higher dose of omeprazole for no added benefit. Furthermore, Zegerid's prescription label already addresses the safety concern for Asian populations by suggesting dose reduction; therefore, consistency should be maintained for Zegerid's OTC label. FDA advised that the safety information contained in the briefing package pertains to only 19 Asian patients and thus would not suffice to address any concerns for a different safety profile in this population. Schering may propose how to address this concern but FDA suggested that one possible approach, in part, might be for Schering to look at WHO data from countries that have a homogeneous Asian population and compare that with overall safety data to identify any potential safety issues in the Asian population. Labeling revision to include a warning statement may still be necessary depending on FDA review of the results of any analysis of omeprazole's safety profile in the Asian population.

3.5 Question 5

Labeling Statement of Identity:
As a result of the discussion at our February 7, 2007 FDA meeting, SPHCP proposed ' as the statement of identity for sodium bicarbonate. b(4)

This is analogous to the function of sodium bicarbonate in Zegerid, which serves as an adjuvant to facilitate the absorption of omeprazole. However, consistent with your recommendation in the Complete Response Letter, and previous precedent established with we now propose as the statement of identity. A mocked up version of the Principal Display Panel is included as Appendix 1. b(4)

Does the Agency agree that the term is acceptable?

FDA Preliminary Response

We do not agree with the use of the term Consumers may mistakenly infer from the term ' rather than merely protecting the omeprazole from degradation. Therefore, using the term may be a misleading. b(4)

In our 1/6/09 complete response letter, we suggested that the statement of identity for sodium bicarbonate read, "Permits absorption of this omeprazole product" and we recommend the use of this statement for the "Purpose" section of Drug Facts and the principal display panel. However, you may propose other wording.

Additional Discussion for Question 5:
Schering acknowledged FDA's concern with the term [redacted] and stated they were looking to shorten FDA's proposed language "permits absorption of this omeprazole product" due to space constraints in the Principal Display Panel (PDP). Schering proposed [redacted] to describe sodium bicarbonate and asked if the statement of identity on the PDP must match that in the Drug Facts. FDA stated that no precedent exists for allowing different language to be used between the statement of identity on the PDP and the "Purpose" statement in Drug Facts and agreed to consider additional labeling proposals. b(4)

3.6 Question 6

Labeling Directions for Use:
SPHCP proposes a minor modification to the Agency proposed directions as follows:

Agency Proposal-

- *Swallow 1 capsule with a glass of water 1 hour before eating in the morning.*

SPHCP Proposal-

- Swallow 1 capsule with a glass of water at least 1 hour before eating in the morning.

Section 14.0 of this document provides the basis for this recommendation, which is consistent with Zegerid Prescription Labeling.

Does the Agency agree with this proposal?

FDA Preliminary Response

We agree that the proposed revised Directions statement is acceptable.

4.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS:

1. Schering will provide details on the pharmacokinetic studies as well as a summary table (or tables) of side-by-side comparisons of the studies to support that the Cmax of Zegerid 20 mg capsule does not exceed the Cmax of omeprazole 40 mg tablet. The CR submission will address the appropriateness of pooling these PK studies. The analysis will also examine pooled individual Cmax values in addition to mean Cmax values.

2. Schering will provide an integrated assessment of safety for Zegerid and omeprazole in the CR, including information from clinical trials, postmarketing data for Zegerid and omeprazole, and an updated literature review. Where relevant, the analysis will utilize appropriate denominators for calculating the frequency of adverse events.

3. Regarding postmarketing information from AERS and WHO databases, Schering will provide a safety analysis proposal for FDA review and comment.

4. Schering will perform additional analyses including an analysis of WHO safety data to address the safety profile in the Asian population. Schering may also propose labeling changes to address safety concerns for the Asian population.

5. Schering will propose alternative statement of identity language for sodium bicarbonate in their complete response.

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

/s/

Joel Schiffenbauer
3/27/2009 08:09:25 AM

From: Schiffenbauer, Joel
To: Lee, Sue Chih H; Chen, Tien Mien; Vienna, Mary R;
cc: Chang, Christina;
Subject: RE: Review of draft CR letter for NDA 22-281/Zegerid OTC capsule
Date: Monday, January 05, 2009 3:47:26 PM

Very good, I understand. thanks.

Joel

From: Lee, Sue Chih H
Sent: Monday, January 05, 2009 3:46 PM
To: Schiffenbauer, Joel; Chen, Tien Mien; Vienna, Mary R
Cc: Chang, Christina
Subject: RE: Review of draft CR letter for NDA 22-281/Zegerid OTC capsule

Joel,

I agree with you. I am not opposing to cross study comparisons if there is something to bridge the studies. For example, if there is a treatment that is common to two studies, then that treatment serves as a link to both studies. I have reservation about doing cross study comparisons simply because of the similarity in study design and assay.

From: Schiffenbauer, Joel
Sent: Monday, January 05, 2009 3:26 PM
To: Chen, Tien Mien; Vienna, Mary R
Cc: Lee, Sue Chih H; Chang, Christina
Subject: RE: Review of draft CR letter for NDA 22-281/Zegerid OTC capsule

Albert,

Thanks for your response. Are you also okay with offering the alternative that the sponsor submit a rationale for their cross study comparison (2b)? I don't think they will be able to provide a satisfactory response but I thought we should give them the opportunity to do so.

Joel

From: Chen, Tien Mien
Sent: Monday, January 05, 2009 2:10 PM
To: Vienna, Mary R
Cc: Schiffenbauer, Joel; Lee, Sue Chih H; Chang, Christina
Subject: RE: Review of draft CR letter for NDA 22-281/Zegerid OTC capsule

Mary: Hi,

The original draft was a little bit confusing to us, so we made "quite a lot of" revisions, but mainly for the drug names. Sorry!

We are OK with the proposed 3-arm PK study, however, I added

1. "under fasted conditions" to the proposed 3-arm PK study to avoid the decreased Cmax of Prilosec OTC 20 mg tablet due to possible food effect and

2. to submit the protocol for review for the 3-arm PK study prior to its initiation if the sponsor agrees.

Lastly, , in the previous OND practice, if the NDA is not approval or approvable (need more study before approval can be made!), they usually don't send labeling comment to the sponsor. Under the new rule, I don't know. Please double check! Thanks!!

<< File: N22281-CR Lttr.Zegerid OTC 20mg Caps-Draft.12-27-08.doc >>

Albert

From: Vienna, Mary R
Sent: Monday, January 05, 2009 10:50 AM
To: Chen, Tien Mien
Cc: Schiffenbauer, Joel; Lee, Sue Chih H; Chang, Christina
Subject: RE: Review of draft CR letter for NDA 22-281/Zegerid OTC capsule

Terrific! I just wanted to draw your attention to that second recommendation and make sure you were OK with it. Thanks so much.....Mary

From: Chen, Tien Mien
Sent: Monday, January 05, 2009 10:49 AM
To: Vienna, Mary R
Cc: Schiffenbauer, Joel; Lee, Sue Chih H; Chang, Christina
Subject: RE: Review of draft CR letter for NDA 22-281/Zegerid OTC capsule

Mary: Hi,

Yes. I am working on it and we will let you know by today. Thanks!!

Albert

From: Vienna, Mary R
Sent: Monday, January 05, 2009 10:48 AM
To: Lee, Sue Chih H; Chen, Tien Mien
Cc: Schiffenbauer, Joel
Subject: FW: Review of draft CR letter for NDA 22-281/Zegerid OTC capsule
Importance: High

Hi Sue & Albert;

Andrea and Joel would like to ensure that Clin/Pharm is OK with the recommendation in item #2 to address the PK deficiencies. If you could indicate concurrence in your email response today, that would be most helpful. Thanks so much.....Mary

---

From: Vienna, Mary R
Sent: Friday, January 02, 2009 2:56 PM
To: Chang, Christina; Shetty, Daiva; Ding, Shulin; Hough, Christopher; Chen, Tien Mien; Lee, Sue Chih H; Tan, Reynold; Chang, Marina Y

Cc: Furness, Melissa; Schiffenbauer, Joel
Subject: Review of draft CR letter for NDA 22-281/Zegerid OTC capsule
Importance: High

Attached is a draft of the CR action letter for NDA 22-281/Zegerid OTC capsule. Per Joel's direction, I used the language in his Summary review, so please ensure the general accuracy of the content. Chris/Sue - if you'd confirm that I identified the correct manufacturing facility, I'd appreciate it. Reynold - I did not include the Asian decent recommendation in the labeling findings, as Joel directed the submission of safety data in the clinical/clin pharm section rather than a label revision.

Please give me your concurrence/comments by COB Monday, Jan 5 - I realize this is a tight timeframe, but we've already communicated most of these issues to the sponsor in the DR letter, and the action letter is due this Friday. Thanks so much.....Mary

<< File: NDA 22-281 CR draft ltr.doc >>

Refer to CMC review for Methods Validation.

Mary R. Vienna

Mary R. Vienna, Regulatory Project Manager

Date: 12/08/08

No meetings were held with the sponsor during Review Cycle 1.

Mary R. Vienna

Mary R. Vienna, Regulatory Project Manager

Date: 12/08/08

No Advisory Committee meeting was held for this application.

Mary R. Vienna

Mary R. Vienna, Regulatory Project Manager

Date: 12/08/08

Hi Bill;

Here are the responses to your questions regarding the safety data.....Mary

FDA: We request submission of the **summary tables** for omeprazole AEs with frequencies **greater than 0.5% of overall AEs** by preferred terms from the Santarus, AERS, WHO databases up to June 21, 2008.

SP: At the time of the submission of the 4-Month Safety Update we only had the data up to June 21, 2008 for the TESS data requested by the Agency. What was available at that time only included data up to December 31, 2007. It is my understanding that these databases are often between 1 and 4 quarters behind in their data entry. We are asking for the most up-to-date data available now. It will take 3 weeks from the request for new WHO or AERS data until receipt of the updated data.

FDA clarification: We are not asking for TESS data. In the interest of time, It is acceptable to provide summary tables for omeprazole AEs frequencies greater than 1.0% of overall AEs from Santarus, AERS and WHO databases up to December 31, 2007.

FDA: We request that the total cases/total adverse events clearly display the following:
One table displaying serious AEs vs. nonserious vs. unknown in both number of reports and % of total from each database.

SP: I want to ensure that the Agency expects one table with 18 columns, e.g.:

	WHO					AERS					SNTS					
	Serious		Non-Serious		Unknown	Serious		Non-Serious		Unknown	Serious		Non-Serious		Unknown	
n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%

FDA clarification: We need three different tables. One for WHO (ex US only), one for AERS, one for SNTS. Each table should have serious vs.. nonserious vs.. unknown in both n and %.

FDA: One table for AEs associated with 20 mg vs. 40 mg vs. 80 mg vs. unknown in both number of reports and % of total from each database.

SP: I want to confirm that this table should be for omeprazole AEs with frequencies greater than 0.5% of overall AEs.

FDA clarification: Yes. Also, it is acceptable to provide omeprazole AEs with frequencies greater than 1.0% of overall AEs.

FDA: One table of AEs stratified by age from each database.

SP: I want to confirm that this table should be for omeprazole AEs with frequencies greater than 0.5% of overall AEs..

FDA clarification: Yes. It is acceptable to provide omeprazole AEs with frequencies greater than 1.0% of overall AEs.

FDA: For the WHO database, we request that these tables address both overall and exUS.

SP: Does the Agency want one table that breaks out the global vs. total AEs? I also want to confirm that this table should be for omeprazole AEs with frequencies greater than 0.5% of overall AEs..

FDA clarification: Please provide one table contrasting total global vs.. exUS AEs. It is acceptable to provide only omeprazole AEs with frequencies greater than 1.0% of overall AEs.

FDA: Please provide a summary and analysis on deaths/serious adverse events by omeprazole dose 20 mg vs. 40 mg for omeprazole postmarketing safety data from FDA/WHO exUS databases (2003-June 13, 2008, encompassing the dates from original submission to the update). Line listing will not suffice.

SP: Is this **all** deaths/serious adverse events or deaths/serious adverse events occurring **with frequency greater than 0.5% of overall AEs**? We want to confirm that by "FDA/WHO ex US" in the request above that the Agency wants summary and analysis on one table with data from AERS and WHO exUS broken down by dose and not two tables (one for 20 mg doses and one for 40 mg doses).

FDA clarification: Please clarify how many deaths/serious AEs there were in FDA database and how many deaths/serious AEs there were in WHO exUS. The information should be broken down by dose.

One table for FDA data, one table for WHO data. e.g.:

	20 mg	40 mg
Death		
SAE		

FDA: We also request the study report for IND 74,284 (CL 2008-02, Zegerid OTC capsule PD study) if it is available.
SP: This study report is not yet available.

FDA: That's fine.

From: Vienna, Mary R
Sent: Monday, September 15, 2008 1:01 PM
To: 'Cochran, William'
Subject: FW: Safety IR for Zegerid NDAs 22-281 b(4)

Hi Bill;

Per your voicemail, I'm resending the additional IR that I sent last week (see below). In addition, please provide a summary and analysis on deaths/serious adverse events by omeprazole dose 20 mg vs. 40 mg for omeprazole postmarketing safety data from FDA/WHO exUS databases (2003-June 13, 2008, encompassing the dates from original submission to the update). Line listing will not suffice. Thanks so much.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

From: Vienna, Mary R
Sent: Tuesday, September 09, 2008 8:26 AM
To: 'Cochran, William'
Subject: Safety IR for Zegerid NDAs 22-281 b(4)

Hi Bill;

I have an information request for additional safety information to be submitted for NDA 22-281 b(4)

We request submission of the **summary tables** for omeprazole AEs with frequencies **greater than 0.5% of overall AEs** by preferred terms from the Santarus, AERS, WHO databases up to June 21, 2008.

We request that the total cases/total adverse events clearly display the following:
One table displaying serious AEs vs. nonserious vs. unknown in both number of reports and % of total from each database.
One table for AEs associated with 20 mg vs. 40 mg vs. 80 mg vs. unknown in both number of reports and % of total from each database.
One table of AEs stratified by age from each database.

For the WHO database, we request that these tables address both overall and exUS.

We also request the study report for IND 74,284 (CL 2008-02, Zegerid OTC capsule PD study) if it is available.

We need this information ASAP. Please contact me if you have any questions. Thanks so much.....Mary

---

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

/s/

Mary R Vienna
12/8/2008 12:20:13 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-281

DISCIPLINE REVIEW LETTER

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Cochran:

Please refer to your new drug application (NDA) dated March 10, 2008 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid® OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules.

We also refer to your submissions dated May 5, August 20, September 29, and October 9, 17, 24, and 28, 2008.

Our review of the Clinical Pharmacology and Clinical sections of your submission is complete, and we have identified the following deficiencies:

1. Zegerid® OTC (20 mg omeprazole & [redacted] mg sodium bicarbonate) capsule is not bioequivalent to Prilosec OTC (omeprazole magnesium 20 mg) tablet. In particular, the mean C_{max} for Zegerid OTC capsule (test) was higher than that of Priolosec OTC tablets (reference), with a 2.2 test/reference ratio (90% confidence interval: 193.3-251.2; n = 134). b(4)

2. Considering that Zegerid 20 mg capsule is more bioavailable than the Prilosec OTC tablet, you have not provided adequate safety data to support this application. The application compares the PK parameters of the Zegerid 20mg capsule with those of the prescription 40 mg Prilosec capsule, which has not been approved for OTC use. This cross-study comparison is not valid, as the two formulations were not compared in a single study, and it is conceivable that the C_{max} of Zegerid 20 mg capsule may be even higher than that of Prilosec 40 mg capsule. Therefore, one cannot bridge the safety of the Zegerid 20mg capsule to the safety data for either 20mg or 40 mg Prilosec formulations.

3. Furthermore, the application does not present any controlled clinical studies directly comparing 20 mg and 40 mg omeprazole with respect to the safety profile, and the postmarketing information analysis is inadequate to refute the difference in safety profiles of 20 mg vs. 40 mg. The AERS data identified a potential safety concern with

acute renal failure events, with a higher frequency of acute renal failure associated with the 40 mg dose compared to the 20 mg formulation (22.92% vs. 18.18%). The WHO Vigibase analysis revealed a higher frequency of thrombocytopenia with the 40 mg dose relative to the 20 mg dose (10.32% vs. 6.8%). These findings may warrant further investigation, but the lack of precise dose information in the databases and the uncontrolled, incomplete and voluntary nature of postmarking reports does not allow for a clear assessment of dose-dependent safety differences.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Mary Vienna, Regulatory Project Manager, at 301-796-4150.

Sincerely,

{See appended electronic signature page}

Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
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/

Andrea Segal
11/26/2008 12:55:39 PM

From: Greeley, George
To: Vienna, Mary R;
cc: Mathis, Lisa;
Subject: NDA 22-281 [redacted] Zegerid OTC
Date: Tuesday, November 25, 2008 10:04:48 AM

b(4)

Mary,

The PeRC has completed it's review of [redacted] applications (capsule [redacted] and agree with Division's request to grant a full waiver.

b(4)

We ask that you modify the pediatric page for NDA 22-281 under Section A to select "other" instead of "Evidence strongly suggests that product would be unsafe in all pediatric subpopulations".

I want to again apologize for my tardiness in relaying the findings from PeRC.

Thanks!

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

1.0 REQUEST FOR WAIVER OF PEDIATRIC STUDIES

NDA NUMBER (as applicable): NDA 22-281

SPONSOR: Schering-Plough HealthCare Products

INDICATIONS: Treatment of frequent heartburn (occurs ***2 or more*** days a week)

1. What age ranges are included in you waiver request?
2. Below 18 years of age
3. Reasons for waiving pediatric studies?
4. No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients.

1.1 Justification for waiver:

In accordance with 21 CFR §314.55(c), the sponsor requests a full waiver from the requirement that the new drug application contain data on the assessment of safety and effectiveness of Zegerid OTC™ Capsules for the claimed indications in pediatric patients.

The sponsor believes that a waiver of the requirement to conduct clinical studies in pediatric patients is justified by virtue of the following:

a) Prilosec (delayed release omeprazole) OTC is currently indicated for adults 18 years of age and older. This 505(b)(2) application for Zegerid relies on the safety and efficacy data for Prilosec OTC.

b) Prilosec OTC obtained a full pediatric waiver based on the fact that "children need to be seen by a physician to diagnose frequent heartburn and should not be self-medicated with this OTC product." (Pediatric Page from the Prilosec OTC review – NDA 21-229).

c) The currently marketed Zegerid Capsule prescription product is not indicated for pediatric patients below the age of 18.

d) The physical size of the capsule dosage form. The composition of the ZEGERID® Capsule formulation requires a capsule shell of 00 size; the dimensions of 00 capsules are summarized below:

- External Diameter, Body: 8.18 mm
- External Diameter, Cap: 8.53 mm
- Overall Closed Length: 23.3 mm

The 00 size capsule is the smallest size that will accommodate the ZEGERID formulation, but a 00 size capsule is not an appropriate dosage form for pediatric patients, especially for pediatric patients < 12 years of age.

e) Assessments of safety and effectiveness of Zegerid OTC™ Capsules in pediatric patients would be very unlikely to reveal any meaningful therapeutic benefit over the existing dosage forms appropriate for pediatric patients.

Schering-Plough

Schering-Plough
56 Livingston Avenue
Roseland, NJ 07068-1733 USA
T 862.245.5197
F 862.245.4041
www.schering-plough.com

Consumer Health Care

William R. Cochran Jr.
Sr. Manager, Regulatory Affairs

October 30, 2008

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Drug Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-281
Zegerid OTC™
Omeprazole/Sodium Bicarbonate
Capsules

Subject: **Amendment:** Documentation of Receipt of Notice to Appropriate Parties of Certification of Invalidity or Noninfringement of Patents

Dear Dr. Leonard-Segal,

Pursuant to 21 CFR 314.52(e), Schering-Plough HealthCare Products, Inc. is amending NDA 22-281, Zegerid OTC™ Omeprazole/Sodium Bicarbonate Capsules to document receipt of notice required under 21 CFR 314.52(a) by each of the parties identified under paragraph (a) of this section and the notification met the requirements of paragraph (c) of this section.

Three parties were notified and two of the parties identified in paragraph (a) of 21 CFR 314.52 sent return receipts, which are attached as Appendix 1 and 2. We did not receive a return receipt from a third recipient of the notice (AstraZeneca LP of Wilmington, DE). In place of a return receipt, I am attaching a paper trail (Appendix 3) that demonstrates that the Notice of Certification of Invalidity or Noninfringement of Patents (sent via Certified Mail on June 6, 2008) was received.

Schering-Plough HealthCare Products, Inc. is certain that the letters were received by AstraZeneca LP of Wilmington, DE because we have received a letter from their outside council requesting information about Zegerid NDAs 22-281 [redacted] In addition to the request for information, I am also attaching in appendix 3 a June 19, 2008 Confidential Disclosure Agreement that was sent to our council. The June 19, 2008 Confidential Disclosure Agreement references all of the parties to which the Notice of Certification of Invalidity or Noninfringement of Patents was sent on June 6, 2008. b(4

45 days have passed since Schering-Plough HealthCare Products, Inc. received return receipts and the June 19, 2008 request for additional information from outside council representing AstraZeneca LLC. From June 19, 2008 the 45 day period ended on August 3, 2008. Schering-Plough HealthCare Products, Inc. provided all documentation requested and no legal action has been taken.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Schering-Plough

Sincerely,

K. Mojeed for

William Cochran

Filed in Duplicate with attachments
Desk Copy to:
CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
This submission contains the following 3 Appendices:

Appendix 1

1. The June 6, 2008 Notice of Certification of Invalidity or Noninfringement of Patents to Aktiebolaget Hassle.
2. The return receipt for our Certification of Invalidity or Noninfringement of Patents to Aktiebolaget Hassle.

Appendix 2

1. The June 6, 2008 Notice of Certification of Invalidity or Noninfringement of Patents to AstraZeneca AB (Sweden).
2. The return receipt for our Certification of Invalidity or Noninfringement of Patents to AstraZeneca AB (Sweden).

Appendix 3

1. The June 6, 2008 Notice of Certification of Invalidity or Noninfringement of Patents to AstraZeneca LP.
2. Certified Mail Receipt for the Certification of Invalidity or Noninfringement of Patents to AstraZeneca LP. 1800 Concord Pike, Wilmington, DE 19803-2902.
3. A letter dated June 19, 2008 from outside legal council requesting information on NDAs 22-281 [redacted], subject of June 6, 2008 Notice of Certification of Invalidity or Noninfringement of Patents from Schering-Plough HealthCare Products, Inc. b(4)
4. The June 19, 2008 Confidential Disclosure Agreement that accompanied the June 19, 2008 request for information from outside legal council representing AstraZeneca LP, Aktiebolaget Hassle, AstraZeneca AB and Merck & Co.,Inc.
5. A June 27, 2008 letter to Schering-Plough HealthCare Products, Inc. explaining from our own outside legal council communicating why the US Postal Service failed to get us a return receipt for the June 6, 2008 notice.
6. A letter dated July 15, 2008 that accompanied CDs containing the information requested by AstraZeneca as a response to our Certification of Invalidity or Noninfringement of Patents to AstraZeneca.

From: Vienna, Mary R
Sent: Wednesday, October 01, 2008 12:50 PM
To: 'Cochran, William'
Subject: Schering's response to last IR

Hi Bill;

We've reviewed Monday's submission, and unfortunately there are still missing items in the analysis. Below is what we still need by the end of this week. The Santarus analysis will also need to be in this format:

AERS--need total number of cases (patients involved) in database.

Table 1, AERS deaths vs. serious vs. non-serious vs. outcome unknown (add another column # of deaths in database)

- Need total # of deaths, total # of cases with serious outcome, total # with non-serious outcome, total # cases with unknown outcome displayed as the last row
- Calculate % of each outcome/total cases

We are still waiting for their analyses of deaths in AERS.

Table 2, AERS data stratified by dose

- Need total # cases (patients) for 10 mg, 20 mg, 40 mg, 80 mg, other, and unknown displayed as the last row
- Calculate % of cases from each dose/total cases

Table 3, AERS data stratified by age

- Need total # cases (patients) for each age group displayed as the last row in table
- Calculate % of cases from each age group/total cases

Repeat same for WHO exUS and Santarus (which we are still waiting for).

If you'd like to speak with the medical officer for clarification, Christina is willing to discuss this further with you. If you need your analysis person in California or in Schering Plough to speak with us, I can arrange a t-con to do so. Thanks.....Mary

---

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

/s/

Mary R Vienna
12/8/2008 12:41:24 PM
CSO

From: Vienna, Mary R
Sent: Monday, October 06, 2008 7:17 AM
To: 'Cochran, William'
Subject: Another IR for the bioequivalence studies: NDA 22-281 (Zegerid OTC 20 mg Caps)

Attachments: N22281-2 IR-3.Zegerid OTC 20 mg Cap BE Study.10-02-08.doc
Hi Bill; Attached is an IR regarding the bioequivalence studies for Zegerid OTC capsules/NDA 22-281. If you can let me know when a response can be expected, that would be helpful to the reviewer.
Thanks.....Mary

Clin Pharm IRs for NDA 22-281 (Zegerid OTC 20 mg Capsules)

10-03-08

1. In the initial bioequivalence (BE) study No. CL2007-03, the % mean ratio for $AUC_{0-\infty}$ values between Zegerid OTC 20 mg capsule (Test) vs. Prilosec OTC 20 mg tablet (Reference) was 0.88 whereas, that value for the pivotal study No. CL2007-15 was 1.16 Discrepancies between the two studies were also observed with C_{max}. Please explain the observed differences.

2. Please explain why the confidence intervals (CI) did not improve as you increased the number of subjects from 35 (Study No. CL2007-03) to 135 (Study No. CL2007-15).

3. In the first BE study (No. CL2007-03), you included all 35 subjects for BE assessments, whereas, in the second BE Study (No. CL2007-15) you could only include 120 subjects for $AUC_{0-\infty}$ calculation when a bump for the mean plasma level at 6 hrs postdose can be seen in both studies. In other words, your analysis included all subjects for $AUC_{0-\infty}$ calculation for Study CL2007-03 but excluded 14 subjects for the pivotal BE study. Please provide your rationale and also the possible reasons for the bump seen at 6 hrs postdose.

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

/s/

Mary R Vienna
12/8/2008 12:46:23 PM
CSO

From: Vienna, Mary R [mailto:Mary.Vienna@fda.hhs.gov]
Sent: Tuesday, September 22, 2009 12:27 PM
To: Cochran, William
Subject: Clarifying question for NDA 22-281/Zegerid OTC application
Importance: High

Hi Bill;

We need a quick clarification on an inconsistency in which studies were referenced in your complete response. Figure 1 on page 12 of appendix 1, volume 1, and Tables 1 & 6 listed different studies as sources of data. Could you clarify the correct citation? Thanks so much.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES
NDA-22281	ORIG-1	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	ZEGERID OTC CAPSULES

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

/s/

MARY RUSSELL R VIENNA
09/23/2009

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-281 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Zegerid OTC Established/Proper Name: Omeprazole and Sodium Bicarbonate Dosage Form: capsule Strengths: 20 mg/1100mg		
Applicant: Shering-Plough Agent for Applicant (if applicable): N/A		
Date of Application: 03-10-08 Date of Receipt: 03-10-08 Date clock started after UN: N/A		
PDUFA Goal Date: 01-10-09	Action Goal Date (if different):	
Filing Date: 05-09-08 Date of Filing Meeting: 04-28-08		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 8		
Proposed Indication(s): Treats frequent heartburn		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☒ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): Division of Gastroenterology Products	
List referenced IND Number(s): No IND referenced, however sponsor has PIND 74,284 for this drug.	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☐ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	☐ YES ☒ NO ☐ YES ☐ NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) **Comments:**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments:**	☐ YES # years requested: ☒ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☐ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☒ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	☐ YES ☒ NO

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☒ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☒ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☐ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☐ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**: Comprehensive index submitted as an application amendment 05-05-08	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☒ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature?	☒ YES ☐ NO

If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge..."* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☒ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
<u>PREA</u> ***Note:*** *NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO ☒ YES ☐ NO

Comments:	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☒ **Not applicable** ☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☐ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not Applicable** ☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☒ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	☒ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☐ YES Date(s): ☒ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☒ YES Date(s): 10-30-07 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 28, 2008

NDA/BLA #: NDA 22-281

PROPRIETARY/ESTABLISHED NAMES: Zegerid OTC capsules/Omeprazole 20mg and sodium bicarbonate 1100 mg

APPLICANT: Schering-Plough

BACKGROUND: This molecular entity is approved as an Rx medication (NDA 21-849), currently submitted as OTC for different indication and population at the 20mg dosage level. Application is 505(b)(2) using NDA 21-229, Prilosec OTC/omeprazole magnesium, as the OTC listed drug.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mary Vienna	Y
	CPMS/TL:	Leah Christl	Y
Cross-Discipline Team Leader (CDTL)	N/A		
Clinical	Reviewer:	Christina Chang Wen-Yi Gao (DGP)	Y Y
	TL:	Daiva Shetty Hugo Gallo-Torres (DGP)	Y Y
Social Scientist Review (*for OTC products*)	Reviewer:	Laura Shay	Y
	TL:	N/A	
Labeling Review (*for OTC products*)	Reviewer:	Reynold Tan	Y
	TL:	Marina Chang	Y
OSE	Reviewer:	Zachary Oleszczuk	Y
	TL:	Todd Bridges	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	

Clinical Pharmacology	Reviewer:	Tien Mien Chen	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:	Same as TL	
	TL:	Mike Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:	N/A	
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Christopher Hough	Y
	TL:	Shulin Ding	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:	N/A	
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:		
Other reviewers	N/A		

OTHER ATTENDEES: Andrea Leonard-Segal, Director, DNCE; Joel Schiffenbauer, Deputy Director, DNCE; Geri Smith, Regulatory Project Manager, DNCE; Darrell Lyons, Regulatory Project Manager, DNCE; Victor Alexander, Medical Officer, DNCE.

505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

Electronic Submission comments **List comments:**	☒ Not Applicable
CLINICAL **Comments:** Application did not contain TESS and DAWN safety data or a comprehensive discussion of the literature related to drug safety.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No clinical studies for this NDA	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:** The application did not contain a comparative dissolution profile of the proposed OTC product and the approved Rx product; and the applicant name was incorrectly listed on the letter of authorization for DMF 1378	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☒ YES ☐ NO

Comments:	
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)**	☐ YES ☒ NO ☐ YES ☐ NO
FACILITY (BLAs only) **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Director, DNCE

GRMP Timeline Milestones: Filing Date: 05-09-08; Day 74: 05-23-08; Review Completion Goal Date: 11-10-08; PDUFA Goal Date: 01-10-09

Comments: Actual PDUFA Goal date 01-09-09 as 01-10-09 is a Saturday

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.

☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

Mary R Vienna
8/20/2008 05:06:01 PM
CSO

From: Vienna, Mary R
Sent: Friday, August 08, 2008 7:31 AM
To: 'Cochran, William'
Subject: Zegerid NDAs safety information request

Hi Bill;

This is the additional safety information request we discussed on the phone.

Schering-Plough mentioned a safety study, OME-IR(SUSP)-C07, which was done at the request of the Division of Gastroenterology Products. FDA requests the full study report of this study. In addition, we request that you submit the full study reports of any available clinical studies conducted with 20 mg and 40 mg Zegerid products.

Thanks.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@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/

Mary R Vienna
12/8/2008 12:03:36 PM
CSO

From: Vienna, Mary R
Sent: Friday, August 08, 2008 7:39 AM
To: 'Cochran, William'
Cc: Lyons, Darrell
Subject: IR for NDA 22-281 (Zegerid OTC 20 mg Tablets)

Hi Bill;

Per our phone conversation, here is the second IR request for one of NDA 22-281's bioequivalence studies:

> To facilitate the review and to verify your conclusion of bioequivalence assessment, please provide 1) the raw PK dataset (individual plasma concentrations and PK parameters) and 2) statistical analysis results of BE assessment of study No. **CL2007-15** in an electronic format.

Thanks very much.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@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/

Mary R Vienna
12/8/2008 12:02:06 PM
CSO

From: Vienna, Mary R [mailto:Mary.Vienna@fda.hhs.gov]
Sent: Tuesday, July 22, 2008 10:57 AM
To: Cochran, William
Subject: RE: Information Request regarding NDA 22-281

Bill; The technical reviewer says that the certification option is OK.....Mary

---

From: Cochran, William [mailto:william.cochran@spcorp.com]
Sent: Thursday, July 17, 2008 3:31 PM
To: Vienna, Mary R
Subject: Information Request regarding NDA 22-281

At the time when we wrote the protocol CL2007-03 we thought that we would be using the Prescription Zegerid(R) Capsules 20 mg. However, the Zegerid OTC Capsules formulation, which is a banded version of the prescription Zegerid(R) Capsules 20 mg was used in both studies. When the protocol was amended to increase the number of subjects from 36 to 136 the Title was not renamed even though the Protocol was amended to call for the banded Zegerid OTC Capsules. That is the reason for the memo (attached) about revising the study report in "Section 2 Synopsis: Title of Study". revised the report to match the title of the study on the protocol.

b(4)

If we are to revise the study report names in the NDA we will need to get approval from the IRB to change the Protocol Name and reissue the repots and in turn resubmit Module 5 all together. We are more than willing to do this but want to be sure that this is what the Agency wants before we do that. Both CL2007-03 and CL2007-15 did use the banded Zegerid OTC Capsules formulation.

I am asking if the Agency wants us to reissue the repots and resubmit Module 5 or submit a certification that Zegerid OTC Capsules were used in both CL2007-03 and CL2007-15 studies and a list of places in the NDA where this may have caused confusion and any other locations where there are references to prescription Zegerid(R) Capsules 20 mg that may cause confusion with respect to these studies. Regardless we will submit replacement pages for the Table of Contents of Module 5 because CL2007-03 did have 36 subjects and not 136. That is a typo.

I apologize for the confusion that this has caused.

<<N22281-1 Zegerid OTC 20 mg Cap Scan-2 (2).pdf>>

Best Regards,
Bill Cochran
Regulatory Affairs

p: 862.245.5197 | f: 862.245.4041 | william.cochran@spcorp.com

Consumer Health Care
Mail Stop 4-R-Blue, 56 Livingston Ave, Roseland, NJ 07068-1733 USA

From: Vienna, Mary R [mailto:Mary.Vienna@fda.hhs.gov]
Sent: Wednesday, July 09, 2008 09:18 AM
To: Cochran, William
Subject: Information Request regarding NDA 22-281
Importance: High

Bill; As per my previous email, we're submitting this information request regarding NDA 22-281.

It is noted that both names, Zegerid 20 mg capsules and Zegerid OTC 20 mg capsules were used (interchangeably) in the NDA submission and it is very confusing. Please see the attached files.

<<N22281-1.Zegerid OTC 20 mg Cap Scan-1.pdf>> <<N22281-1.Zegerid OTC 20 mg Cap Scan-2.pdf>>

Please clarify as to which Zegerid formulation (prescription 20 mg capsule or OTC 20 mg capsule) was actually used in the bioequivalence studies submitted to NDA 22-281. Please provide correction pages if necessary.

Please let me know when a response will be ready. Thanks so much.

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@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/

Mary R Vienna
12/8/2008 11:21:47 AM
CSO

From: Vienna, Mary R
Sent: Thursday, July 10, 2008 11:56 AM
To: 'Cochran, William'
Cc: Christl, Leah A
Subject: RE: Paragraph IV Patent Certification Amendment

Bill; We looked into the situation, and the 45-day clock starts the day after the patent holders (including AstraZeneca) receive the notice, not when you submit the return receipts to the FDA (per 314.52(f)). So the 45-day start date is one day after the date of receipt posted on the return receipts. It's Schering-Plough's responsibility to monitor that time and to notify us if any legal action is taken.

314.52(e) requires that we receive documentation of receipt by either return receipt or by a letter acknowledging receipt before we can approve the application. In the case of AstraZeneca, you can either submit the signed receipt when you get it, or you can get a letter from them acknowledging receipt.

I hope you find this helpful.....Mary

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@fda.hhs.gov

From: Cochran, William [mailto:william.cochran@spcorp.com]
Sent: Wednesday, July 09, 2008 9:48 AM
To: Vienna, Mary R
Subject: Zegerid OTC Capsules ←——— Paragraph IV Notifications b(4)

I was wondering if you have had a chance to discuss my Paragraph IV Amendments with Leah.

Was the submission sufficient to start the 45 day clock and if so can you tell me what that start date is?

If it was insufficient, do I need to provide more information about the AstraZeneca US notification?

From: Cochran, William [mailto:william.cochran@spcorp.com]
Sent: Wednesday, July 02, 2008 7:20 PM
To: Vienna, Mary R
Subject: Paragraph IV Patent Certification Amendment

Mary, attached is a copy of one of the Paragraph IV Return Receipts Amendment. I sent desk copies of both Capsule ←——— to you via fed-ex. b(4)

I may have made a mistake in this submission in that I stated that "as of today, July 2, 2008" we have received all but one return receipts from the patent holders. Our problem is that AstraZeneca (US) never sent our return receipt back. Included in the submission is a letter from our lawyer explaining what the

US Postal Service gave as a reason that we have not yet received it. Apparently all certified mail goes to AstraZeneca (US) in bulk and Astra's mail room sends the return receipts back when they get around to it. Amongst the other recipients of the notifications is AstraZenica (Sweden) and we do have confirmation that they received the notifications on June 10th.

We received questions from AstraZeneca's legal council about our applications via a fax on June 19 from their outside legal council to our outside patent legal council. So we know that they received the notification and are aware of it. I did not include that fax in my submission because at the time it didn't seem like any pertinent information. There is nothing in it that we want to hide from the Agency it is a request for DMFs and Drug Manufacturing information, which we are preparing for them.

In my submission I sated that as of today, July 2, 2008 we have received all but one of the return receipts and explained the one that I do not yet have. Should I have stated as of June 19th, we received all but one receipt? I want to make sure that I start the 45 day clock from the right place. Can you give me any guidance?

I do not know why I sent the submission before asking this question. On my train ride home I pondered the situation and realized that I should probably have dated it when we got the fax from AstraZeneca's legal council as that was the last date, rather than "as of today". I apologize for the confusion. 505(b)(2)s are new to me and to Schering.

If I need to send another amendment and include the fax I will gladly do so if that helps. I'm not sure if what I provided is unclear.

<<DOC001.PDF>>

Best Regards,
Bill Cochran
Regulatory Affairs

p: 862.245.5197 | f: 862.245.4041 | william.cochran@spcorp.com

---

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

/s/

Mary R Vienna
12/8/2008 11:37:05 AM
CSO

KENYON & KENYON LLP
Intellectual Property Law

Charles A. Weiss
Direct 212.908.6287
cweiss@kenyon.com

One Broadway
New York, NY 10004-1007
212.425.7200
Fax 212.425.5288

July 15, 2008

By Hand

Errol B. Taylor, Esq.
Milbank, Tweed, Hadley & McCloy LLP
1 Chase Manhattan Plaza
New York, NY 10005-1413

b(4)

Re: NDA Nos. 22-281

Dear Mr. Taylor:

I enclose herewith, under the scope of the Confidential Disclosure Agreement between Schering-Plough Healthcare Products and your clients, CDs with the above-referenced NDAs.

Very truly yours,

Charles A. Weiss

smm
Enclosure

From:	Vienna, Mary R
To:	"Cochran, William";
CC:	
Subject:	Information Request regarding NDA 22-281
Date:	Wednesday, July 09, 2008 9:18:10 AM
Attachments:	N22281-1.Zegerid OTC 20 mg Cap Scan-1.pdf N22281-1.Zegerid OTC 20 mg Cap Scan-2.pdf

Bill; As per my previous email, we're submitting this information request regarding NDA 22-281.

It is noted that both names, Zegerid 20 mg capsules and Zegerid OTC 20 mg capsules were used (interchangeably) in the NDA submission and it is very confusing. Please see the attached files.

Please clarify as to which Zegerid formulation (prescription 20 mg capsule or OTC 20 mg capsule) was actually used in the bioequivalence studies submitted to NDA 22-281. Please provide correction pages if necessary.

Please let me know when a response will be ready. Thanks so much.

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@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/

Mary R Vienna
7/23/2008 07:37:23 AM
CSO

Schering-Plough

Schering-Plough
56 Livingston Avenue
Roseland, NJ 07068-1733 USA
T 862.245.5197
F 862.245.4041
www.schering-plough.com

Consumer Health Care

William R. Cochran Jr.
Sr. Manager, Regulatory Affairs

DUPLICATE

ORIGINAL AMENDMENT

July 2, 2008

N-000-PD

Andrea Leonard-Segal, MD, Director
Division of Nonprescription Drug Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-281
Zegerid OTC™
Omeprazole/Sodium Bicarbonate
Capsules

Subject: **Amendment**- Documentation of Receipt of Notice to Appropriate Parties of Certification of Invalidity or Noninfringement of Patents

Dear Dr. Leonard-Segal,

Pursuant to 21 CFR 314.52(e), Schering-Plough HealthCare Products, Inc. is amending NDA 22-281, Zegerid OTC™ Omeprazole/Sodium Bicarbonate Capsules to document receipt of the notice required under 21 CFR 314.52(a). As of July 2, 2008 a return receipt for all but one notification was confirmed from each person identified under paragraph (a) of this section and the notification met the requirements of paragraph (c) of this section.

The one return receipt that we have yet to receive is from the United States AstraZeneca LP of Wilmington, DE address. We know that the letters were received by AstraZeneca because we have received a letter from their outside council asking for additional information about this product. I am attaching a letter documenting the shipment of the certification to AstraZeneca LP.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

Sincerely,

William Cochran

William Cochran

Filed in Duplicate with attachments

Desk Copy to:
CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager

Letter 1

KENYON & KENYON LLP
Intellectual Property Law

Charles A. Weiss
Direct 212.908.6287
cweiss@kenyon.com

One Broadway
New York, NY 10004-1007
212.425.7200
Fax 212.425.5288

June 27, 2008

By E-mail and
Confirmation by First Class Mail

Matthew J. Golden, Esq.
Patent Director
Schering-Plough Corporation
Patent Department K-6-1 1990
200 Galloping Hill Road
Kenilworth, NJ 07033-0530

Re: Zegerid OTC (20 mg Omeprazole & 1100 mg. Sodium bicarbonate) capsules

Dear Matt:

In response to your request, I set forward the following:

- On June 6, 2008, the Patent Certification Notice letter was mailed by U.S. Postal Service, Certified Mail/Return Receipt Request No. 7003 0500 0002 2920 5331 to AstraZeneca LP at 1800 Concord Pike, Wilmington, DE 19803-2902. A signed Return Receipt has yet to come back to our offices. On June 24, 2008, an investigation was initiated with the Post Office in New York which referred us to the Post Office in Wilmington. My secretary spoke to a supervisor at that Post Office, who advised that mail (including certified mail) is delivered to AstraZeneca in bulk and that certified mail is delivered without requiring a signature. Supposedly, the AstraZeneca mail room will eventually provide signatures on return receipt cards, but the regular carrier is on vacation so there is no way to check. For your records, attached is a copy of the receipt showing that the letter to Wilmington was in fact mailed.

- The Patent Certification Notice letter was also sent on June 6, 2008 by U.S. Postal Service, Registered Mail/Return Receipt to Aktiebolaget Hassle at SE – 151 85 Sodertalje in Sweden (RA 676 419 195 US) and to AstraZeneca AB at SE – 151 85 Sodertalje, Sweden (RA 676 419 200 US). The signed receipts returned showing delivery on June 10, 2008.

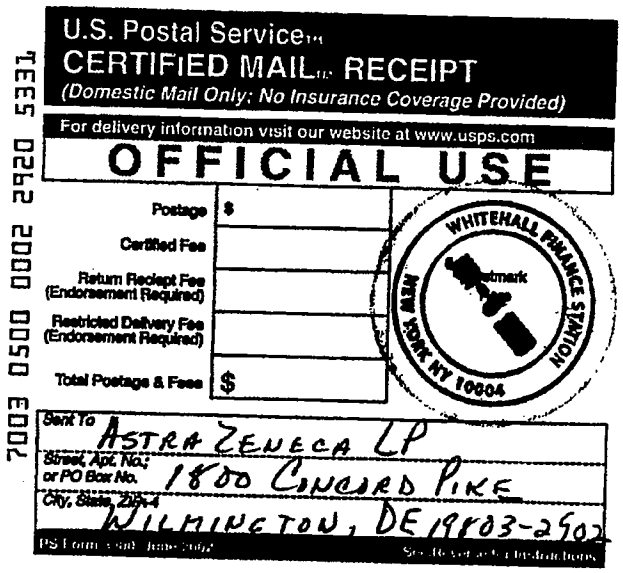
- We know that the letters were received by AstraZeneca because we got a letter from its outside counsel (Errol Taylor of Milbank Tweed) asking for additional information about the products.

Please call me if you have any further questions.

Sincerely yours,

Charles A. Weiss

:smm
Enclosure


U.S. Postal Service
CERTIFIED MAIL RECEIPT
(Domestic Mail Only; No Insurance Coverage Provided)
For delivery information visit our website at www.usps.com
OFFICIAL USE
Postage $
Certified Fee
Return Receipt Fee (Endorsement Required)
Restricted Delivery Fee (Endorsement Required)
Total Postage & Fees $
WHITEHALL FINANCE STATION
NEW YORK NY 10004
Sent To ASTRA ZENECA LP
Street, Apt. No.; or PO Box No. 1800 CONCORD PIKE
City, State, ZIP+4 WILMINGTON, DE 19803-2902
7003 0500 0002 2920 5331

Letter 2

Completed by the office of origin. (A remplir par le bureau d'origine.)

Item Description (Nature de l'envoi) ☒ Registered Article (Envoi recommandé) ☐ Letter (Lettre) ☐ Printed Matter (Imprimé) ☐ Other (Autre) ☒ Recorded Delivery (Envoi à livraison attestée) ☐ Express Mail International

☐ Insured Parcel (Colis avec valeur déclarée) | Insured Value (Valeur déclarée) | Article Number: RA 676 419 195 US

Office of Mailing (Bureau de dépôt) | Date of Posting (Date de dépôt)

Addressee Name or Firm (Nom ou raison sociale du destinataire)
Aktiebolaget Hassle

Street and No. (Rue et No.)
SE - 151 85

Place and Country (Localité et pays)
Södertälje, SWEDEN

Completed at destination. (A compléter à destination.)

This receipt must be signed by: (1) the addressee; or, (2) a person authorized to sign under the regulations of the country of destination; or, (3) if those regulations so provide, by the employee of the office of destination. This signed form will be returned to the sender by the first mail.
(Cet avis doit être signé par le destinataire ou par une personne y autorisée en vertu des règlements du pays de destination, ou, si ces règlements le comportent, par l'agent du bureau de destination. Il renvoyé par le premier courrier directement à expéditeur).

Postmark of the office of destination (Timbre du bureau de destination)

☐ The article mentioned above was duly delivered. (L'envoi mentionné ci-dessus a été dûment livré.) | Date: June 10, 2008

Signature of Addressee (Signature du destinataire) | Office of Destination Employee Signature (Signature de l'agent du bureau de destination)

PS Form 2865, February 1997 (Reverse)

UNITED STATES POSTAL SERVICE

Return Receipt for International Mail
(Registered, Insured, Recorded Delivery, Express Mail)

Administration des Postes des Etats-Unis d'Amérique

Par Avion

Postmark of the office returning the receipt *Timbre du bureau renvoyant l'avis*

Return by the quickest route (air or surface mail), a découvert and postage free.

A renvoyer par la voie la plus rapide (aérienne ou de surface), à découvert et en franchise de port.

The sender completes and indicates the address for the return of this receipt.
(A remplir par l'expéditeur, qui indiquera son adresse pour le renvoi du présent avis.)

Name or Firm (Nom ou raison sociale)
CHARLES A. WEISS

KENYON & KENYON
Street and Number (Rue et no.)
ONE BROADWAY
City, State, and ZIP + 4 (Localité et code postal)
NEW YORK, NY 10004-1007

UNITED STATES OF AMERICA — Etats-Unis d'Amérique

PS Form **2865**, February 1997 — ***Avis de réception*** — **CN07** *(Old C5)*

Letter 3

Completed by the office of origin. (A remplir par le bureau d'origine.)

Registered Article (Envoi recommandé)
☐ Letter (Lettre) ☐ Printed Matter (Imprimé) ☐ Other (Autre)
☐ Recorded Delivery (Envoi à livraison attestée) ☐ Express Mail International

☐ Insured Parcel (Colis avec valeur déclarée)
Insured Value (Valeur déclarée)
Article Number: RA 676 419 200 US

Office of Mailing (Bureau de dépôt)
Date of Posting (Date de dépôt)

Addressee Name or Firm (Nom ou raison sociale du destinataire)
ASTRAZENECA AB
Street and No. (Rue et No.)
SE-151 85 Södertälje
Place and Country (Localité et pays)
SWEDEN

Completed at destination. (A compléter à destination.)

This receipt must be signed by: (1) the addressee; or, (2) a person authorized to sign under the regulations of the country of destination; or, (3) if those regulations so provide, by the employee of the office of destination. This signed form will be returned to the sender by the first mail.
(Cet avis doit être signé par le destinataire ou par une personne y autorisée en vertu des règlements du pays de destination, ou, si ces règlements le comportent, par l'agent du bureau de destination, et renvoyé par le premier courrier directement à expéditeur).

Postmark of the office of destination (Timbre du bureau de destination)
S-LEPSE
Poste bebit

☐ The article mentioned above was duly delivered. (L'envoi mentionné ci-dessus a été dûment livré.)
Date: June 10, 2008

Signature of Addressee (Signature du destinataire)
Office of Destination Employee Signature (Signature de l'agent du bureau de destination)

PS Form 2865, October 1992 (Reverse)

Administration des Postes des Etats-Unis d'Amérique

Return Receipt for International Mail

(Registered, Insured, Recorded Delivery, Express Mail)

Avis de réception

Par Avion

Postmark of the office returning the receipt (Timbre du bureau renvoyant l'avis)

C5

Return by the quickest route (air or surface mail), à découvert and postage free.

A renvoyer par la voie la plus rapide (aérienne ou de surface), à découvert et en franchise de port.

The sender completes and indicates the address for the return of this receipt (A remplir par l'expéditeur, qui indiquera son adresse pour le renvoi du présent avis.)

Name or Firm (Nom ou raison sociale)
CHARLES A. WEISS

KENYON & KENYON
Street and Number (Rue et no.)
ONE BROADWAY
City, State, and ZIP + 4 (Localité et code postal)
NEW YORK, NY 10004-1007

UNITED STATES OF AMERICA — Etats-Unis d'Amérique

PS Form 2865, October 1992

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Office/Division): OND/PMHS

FROM (Name, Office/Division, and Phone Number of Requestor): Mary R. Vienna, DNCE 301-796-4150

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
18-Jun-06		22-281	new NDAs	10-Mar-08 (NDA 22-281) b(4)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zegerid OTC	Standard		18-Aug-08

NAME OF FIRM: Schering-Plough

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☒ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 22-281 (Zegerid OTC capsule) b(4)

seeking indication "treatment of frequent heartburn " by relying on data from the Prilosec OTC switch application. The Applicant requests waiver for pediatric population below 18 years of age. The Sponsor's stated reasons for the waiver are: 1) there would be no meaningful therapeutic benefit over existing treatments and 2) it would be unlikely for the products to be used in a substantial number of pediatric patients. The Sponsor further provided the following justifications for the waiver:

1) Prilosec OTC is currently indicated for adults 18 years of age and older. These 505 (b)(2) applications rely on the safety and efficacy data for Prilosec OTC.

2) Prilosec OTC was granted a full pediatric waiver based on the fact that "children need to be seen by a physician to diagnose frequent heartburn and should not be self-medicated with this OTC product." (Pediatric Page from the Prilosec OTC review - NDA 21-229).

The currently marketed prescription Zegerid capsules and powder products are not indicated for pediatric patients below the age of 18.

4) Assessments of safety and effectiveness of Zegerid OTC capsules in pediatric patients would be very unlikely to reveal any meaningful therapeutic benefit over the existing dosage forms b(4)

appropriate for pediatric patients.

Question:

Given that the these applications do trigger PREA because of the OTC indication (frequent heartburn vs. prescription indication GERD),

should studies in the pediatric population be required for these NDAs? b(4)

Attachments: cover letters, clinical summaries, waiver justifications, NDA 21-229 pediatric page emailed to PMHA

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Mary R. Vienna x64150	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

Mary R Vienna
6/24/2008 02:47:52 PM

MILBANK, TWEED, HADLEY & McCLOY LLP

1 CHASE MANHATTAN PLAZA

NEW YORK, N.Y. 10005-1413

212-530-5000

FAX: 212-530-5219

LOS ANGELES
213-892-4000
FAX: 213-629-5063

WASHINGTON, D.C.
202-835-7500
FAX: 202-835-7586

LONDON
020-7615-3000
FAX: 020-7615-3100

FRANKFURT
49-69-71914-3400
FAX: 49-69-71914-3500

MUNICH
49-89-25559-3600
FAX: 49-89-25559-3700

BEIJING
8610-5123-5120
FAX: 8610-5123-5191

HONG KONG
852-2971-4888
FAX: 852-2840-0792

SINGAPORE
65-6428-2400
FAX: 65-6428-2500

TOKYO
813-3504-1050
FAX: 813-3595-2790

ERROL B. TAYLOR
PARTNER
DIRECT DIAL NUMBER
212-530-5545
FAX: 212-822-5545

June 19, 2008

BY FACSIMILE AND FIRST CLASS MAIL
Charles A. Weiss, Esq.
Kenyon and Kenyon
One Broadway
New York, NY 10004

Re: NDA Nos. 22-281 Notice Letters dated June 6, 2008 b(4)

Dear Mr. Weiss:

As outside counsel to AstraZeneca and Merck, I write in response to your Notice Letters dated June 6, 2008, regarding Schering-Plough Healthcare Products, Inc.'s ("SP") NDA No. 22-281 to commercially manufacture ZEGERID® OTC (20 mg omeprazole and 1100 mg sodium bicarbonate) capsules (the "Zegerid OTC capsules")

I also respond to the b(4)
Offer of Confidential Access to Application that accompanied the letters.

As an initial matter, we request that SP provide AstraZeneca and Merck access to confidential materials pursuant to the same terms as set forth in the July 15, 2005 Confidential Disclosure Agreement for Santarus' NDA No. 21-849, as amended by the parties, and the August 5, 2005 Confidential Disclosure Agreement for Santarus' NDA Nos. 21-849 and 21-850 for ZEGERID® capsules and chewable tablets. Enclosed is a copy of the proposed Confidential Disclosure Agreement. If the terms are acceptable, please countersign and return the CDA to me.

SP's present Confidential Offers are limited to portions of NDA Nos. 22-281 b(4)
selected by SP. AstraZeneca and Merck request the following additional documents to further investigate the representations made by you in the SP June 6 Notice Letters.

(1) A complete copy of NDA No. 22-281, including all correspondence with the FDA relating to the Zegerid OTC capsules;

(2) The DMFs for the active ingredient of the product described in NDA No. 22-281;

(3) Results of any [redacted] testing and any [redacted] studies of the omeprazole used in the Zegerid OTC capsules and of SP's omeprazole formulations; b(4)

(4) [redacted] b(4)

(5) [redacted] b(4)

(6) [redacted] b(4)

Our agreement to accept this information and these materials is not a concession that the information and materials are sufficient to address the accuracy of the statements in the SP June 6 Notice Letters. AstraZeneca requests that the materials be shipped to me as soon as possible.

Very truly yours,

Errol B. Taylor

Enclosures

CONFIDENTIAL DISCLOSURE AGREEMENT

June 19, 2008

This Confidential Disclosure Agreement ("CDA") shall cover any information, samples or other materials provided regarding the Schering-Plough Healthcare Products, Inc.'s ("SP") Products that are the subject of NDA Nos. 22-281 ~~~~ (the "SP Product Information"). SP may (but is not obligated to) provide certain SP Product Information to AstraZeneca LP, Aktiebolaget Hassle and AstraZeneca AB (collectively "AstraZeneca"), Merck & Co., Inc. ("Merck"), and their counsel. AstraZeneca and Merck agree to maintain the SP Product Information in confidence and to use the SP Product Information only to evaluate the representations made in the SP Notice Letters dated June 6, 2008 with respect to the products and patents referred to therein, and not for any other purpose. This agreement does not operate to restrict the use of any information that AstraZeneca and Merck may receive in discovery in the course of any future litigation between the parties. The restrictions of this agreement shall not apply to SP Product Information that was (a) in the public domain before it was disclosed by SP to AstraZeneca and Merck; (b) in the public domain subsequent to its disclosure by SP through no act, or failure to act, of AstraZeneca and Merck; or (c) in the legal possession of AstraZeneca and Merck before its disclosure by SP.

b(4)

AstraZeneca and Merck will limit access to the SP Product Information to the following persons:

(1) Milbank, Tweed, Hadley & McCloy LLP, outside counsel for AstraZeneca and Merck;

(2) Jeffrey Pott, Assistant General Counsel for AstraZeneca;

(3) Marcus Heifetz, Senior Counsel for AstraZeneca;

(4) Katarina Ageborg, Assistant General Counsel for AstraZeneca;

(5) William Krovatin, Counsel for Merck;

(6) Karin Lovquist, Ph.D., AstraZeneca employee: Associate Principal Scientist;

(7) Bo Ingvar Ymen, Ph.D., AstraZeneca employee: Principal Scientist;

(8) Mark Nicholas, AstraZeneca employee: Senior Scientist;

(9) Per Lindberg, AstraZeneca employee: Scientist;

(10) Joacim Gustafsson, AstraZeneca employee: Scientist;

(11) Frans Langkilde, AstraZeneca employee: Scientist;

(12) Third party expert consultants to be identified before disclosure of any SP Product Information.

Each permitted recipient of the SP Product Information listed above will receive a copy of this CDA and agree to be bound by its terms before receiving any SP Product Information, SP will mark the SP Product Information to indicate that it is subject to this agreement, AstraZeneca and Merck agree not to use this CDA to argue that the above AstraZeneca employees, or any other person, or any category of persons should be permitted access in the future to confidential information for any purpose, including without limitation, confidential information provided under a protective order in connection with any litigation.

ACCEPTED AND AGREED

Errol B. Taylor
Counsel for AstraZeneca and Merck

Charles A. Weiss
Counsel for Schering-Plough Healthcare Products, Inc.

KENYON & KENYON LLP
Intellectual Property Law

Charles A. Weiss
Direct 212.908.6287
cweiss@kenyon.com

One Broadway
New York, NY 10004-1007
212.425.7200
Fax 212.425.5288

June 6, 2008

Certified Mail/Return Receipt Requested
Return Receipt No. 7003 0500 0002 2920 5331:

AstraZeneca LP
1800 Concord Pike
Wilmington, DE 19803-2902

Registered Mail/Return Receipt Requested
Return Receipt No. 676 419 173 US:

Aktiebolaget Hassle
SE – 151 85 Södertälje
Sweden

Registered Mail/Return Receipt Requested
Return Receipt No. RA 676 419 187:

AstraZeneca AB
SE – 151 85 Södertälje
Sweden

Re: Patent Certification Notice – U.S. Patent Nos. 4,786,505, 4,853,230, 5,690,960, 5,753,265, 5,817,338, 5,900,424, 6,403,616, and 6,428,810
Zegerid® OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules
Section 505(b)(2) NDA No. 22-281

To Whom It May Concern:

The purpose of this communication is to provide the notice and information required by 21 U.S.C. § 355(b)(3)(A) and (B) (sections 505(b)(3)(A) and (B) of the Food, Drug and Cosmetic Act) that Schering-Plough Healthcare Products, Inc. ("SP"), a Delaware corporation with offices at 556 Morris Avenue, Summit, NJ 07901, has submitted a New Drug Application pursuant to 21 U.S.C. § 355(b)(2) (section 505(b)(2) of the Food, Drug, and Cosmetic Act) for the above referenced drug product which contains the required bioavailability and/or bioequivalence data and a Paragraph iv certification with respect to U.S. Patent Nos. 4,786,505, 4,853,230, 5,690,960, 5,753,265, 5,817,338, 5,900,424, 6,403,616, and 6,428,810 ("the listed patents").

SP submits its Paragraph iv certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv), which asserts that the listed patents listed in the FDA Orange Book for Prilosec® OTC (omeprazole magnesium delayed release) are invalid, unenforceable or not infringed by the commercial manufacture, use or sale of Zegerid® OTC (20 mg omeprazole and 1100 mg sodium bicarbonate) capsules.

To obtain approval to engage in the commercial manufacture, use, or sale of its proposed product before expiration of the listed patents, SP has submitted and the FDA has filed the above-identified application.

The bases of SP's opinion are set forth in detailed statement enclosed herewith. For the reasons stated therein, it is SP's opinion that all claims of the listed patents are invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of SP's proposed product. SP reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these U.S. Patents are invalid, unenforceable, or not infringed.

Pursuant to 21 U.S.C. § 355(c)(3)(D), SP offers confidential access to the application on the terms provided in the enclosed document.

Very truly yours,

Charles A Weiss (RS)

Charles A. Weiss

:smm
Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-281

Schering-Plough Healthcare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Cochran:

Please refer to your new drug application (NDA) dated March 10, 2008, received March 10, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zegerid® OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules.

We also refer to your submissions dated April 25, 2008 and May 5, 2008.

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 10, 2009.

During our filing review of your application, we identified the following potential review issues:

1. The application did not contain safety data from the National Poisoning and Exposure Database (TESS) or from the Drug Abuse Warning Network (DAWN) database.
2. The application did not include a comprehensive discussion of the literature related to drug safety for this NDA.
3. The application did not contain a comparative dissolution profile of the proposed OTC product and the approved Rx product.
4. The application did not contain a proper letter of authorization with a correct applicant name on the DMF (Schering/Plough instead of Schering Corporation). 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.

We also request that you submit the following information:

1. Safety data from the TESS and DAWN databases with the 4-month safety update.
2. Translated labeling for Zegerid products from foreign countries where they are marketed without a prescription and identification of whether the particular labeling is for OTC or pharmacy-only/behind-the-count marketing.
3. A comprehensive discussion of the literature related to drug safety for this NDA.
4. A comparative dissolution profile of the proposed OTC product and the approved Rx product.
5. Drug Facts labeling in Word format.
6. A corrected DMF —. b(4)

Please respond only to the above requests for additional 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.

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 for pediatric patients below 18 years of age. 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 Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
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/

Joel Schiffenbauer
5/16/2008 08:45:28 AM
for Dr. Leonard-Segal

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: May 06, 2008

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Dennis Bashaw, Pharm.D — 5/6/08
Director, Division of Clinical Pharmacology 3, OCP/OTS

FROM: Mary Vienna
Regulatory Project Manager, Over-The-Counter Drug Products, HFD-560

SUBJECT: Request for Biopharmaceutical Inspections
NDA 22-281
Zegerid (Omeprazole/Sod. Bicarbonate) OTC 20 mg Capsules

The following studies/sites pivotal to approval have been identified for inspection:

Study Title: A Single Dose, Comparative, Randomized, Crossover Bioequivalence Study of Omeprazole Administered as Zegerid Capsules 20 mg and Prilosec OTC™ Delayed-Release Tablets 20 mg in 136 Healthy Subjects

Study #	**Clinical Site (name, address, phone, fax, contact person, if available)**	**Analytical Site (name, address, phone, fax, contact person, if available)**
CL2007-15		

b(4)

GOAL DATE FOR COMPLETION:

We request that the inspections be conducted and the Inspection Summary Results be provided by October 10, 2008.

Should you require any additional information, please contact Mary Vienna at 301-796-4150.

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

/s/

Mary R Vienna
5/13/2008 09:17:06 AM

Vienna, Mary R

From: Vienna, Mary R
Sent: Friday, May 02, 2008 8:04 AM
To: 'Cochran, William'
Cc: Smith, Geri; Chang, Christina; Shetty, Daiva
Subject: RE: NDA 22-281 _____ Action Plan

b(4)

Bill; We have reviewed the content of your action plan and find it acceptable. Please submit the information by Monday for both NDAs as we discussed - the timing proposed below for submission is not acceptable. Thanks.....Mary

---

From: Cochran, William [mailto:william.cochran@spcorp.com]
Sent: Thursday, May 01, 2008 1:11 PM
To: Vienna, Mary R
Subject:

Mary, we no longer have the stratification question that I mentioned to you this morning. Here is our action plan in response to your communication Monday.

We will be amending Module 5 to include an ISS for both NDAs.

We will be updating the original summary of safety that was provided in Module 2 to include a separate review and analysis of the postmarketing databases (Santarus, WHO and AERS) stratified as requested where the databases support such stratification.

This will be in addition to the overall analysis and review already included in Module 2 sections 2.7.2 and 2.7.4.

The ISS will include separate sections that include:

* QT/QTc information
* A summary of the literature that is available on drug-drug interactions for both omeprazole and sodium bicarbonate

* We will be making a commitment to provide safety data from the National Poisoning and Exposure Database (TESS) and data from Drug Abuse Warning Network (DAWN).

For the sake of clarity, I want to confirm the location of the ISS in Module 5. You had mentioned in your e-mail on Monday 5.3.6 but the current CTD guideline shows that the ISS should be located in 5.3.5? Will you confirm

You asked for this information by close of business Friday and we are requesting that we be allowed to send this first thing Monday morning instead of close of business Friday. We will provide you first thing Monday morning the text of the ISS for the Capsules NDA (22-281) via e-mail and follow up with a submission with the text, tables, and attachments.

The ISS information that we will be adding for both NDAs is essentially the same. Since the Capsule NDA (22-281) filing date is May 9. _____ we propose that we be allowed to provide the Capsule information on Monday _____

b(4)

We want to work with the Agency collaboratively to get all of the information necessary to support ~~NDA~~ Please let me know if there is anything that I can provide.

b(4)

Best Regards,
Bill Cochran
Regulatory Affairs
Schering-Plough HealthCare Products, Inc.
556 Morris Avenue
S-4-2 Mail Stop 2180
Summit, NJ 07901-1330
T (908) 473-1858
F (908) 473-1741

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

/s/

Mary R Vienna
5/2/2008 11:28:28 AM
CSO

Vienna, Mary R

om: cderdocadmin@cder.fda.gov
nt: Wednesday, April 30, 2008 1:38 PM
o: Vienna, Mary R
Subject: DFS Email - N 022281 N 000 10-Mar-2008 - Review (noted no comments - NAI)

Document room close out the following assignments:

		Personnel Code	Sup-Concur	St
N 022281 N 000	10-Mar-2008	E86	30-Apr-2008	NR

Document Type: Review (noted no comments - NAI)
Submission Description:

Author(s)/Discipline(s)

1. Mike Welch, BIOMETRICS

Signer(s)

1. Mike Welch
   No new clinical studies submitted. DB3 statistical review not required.
   30-Apr-2008

Vienna, Mary R

From: Vienna, Mary R
Sent: Tuesday, April 29, 2008 9:33 AM
To: 'Cochran, William'
Cc: Smith, Geri; Chang, Christina; Shetty, Daiva; Schiffenbauer, Joel; Leonard Segal, Andrea; Christl, Leah A
Subject: NDA 22-281 [redacted] b(4)
Importance: High

Bill;

Per my voicemail to you this morning, we identified the following deficiency during our preliminary review of your submissions: the Integrated Summary of Safety (ISS) section is not included in Module 5 of either NDA. The ISS must be located in Module 5 (section 5.3.6) of each NDA. The clinical summary in Module 2 does not take the place of the integrated summaries in Module 5. Before we can file each NDA, you must provide an ISS incorporating the following information:

1. Postmarketing adverse event reports collected by Santarus for both 20 mg and 40 mg Zegerid products, accompanied by a safety analysis. Also describe the method/system by which these data are collected.

2. A description of the proarrhythmic potential of this product. Refer to ICH guidance for industry E14 *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.*

3. Data and an analysis of drug-drug interactions (for both omeprazole and sodium bicarbonate).

4. Safety data from the National Poisoning and Exposure Database (TESS) as well as data from Drug Abuse Warning Network (DAWN) database. (In this case, it is acceptable to commit to provide information from these two databases with the 4-month safety update.)

Further, the safety information you did include in the original submissions of the NDAs was submitted in tabular form or as line-listings. This is insufficient. All safety databases must be accompanied by an analysis and a summary. All safety analyses should be stratified by chronology, dose, demographics, severity and seriousness, relation to the drug, and drug-drug interactions.

Provide this information by close-of-business Friday, May 2.

CAPT Mary R. Vienna, R.N., M.H.A.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
OND/CDER/FDA
10903 New Hampshire Avenue
Bldg. 22, Room 5481
Silver Spring, MD 20993
301-796-4150
Mary.Vienna@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/

Mary R Vienna
5/2/2008 11:23:21 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-281

NDA ACKNOWLEDGMENT

Schering-Plough HealthCare Products, Inc.
Attention: William Cochran
Senior Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Cochran:

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

Name of Drug Product: Zegerid® OTC (20 mg omeprazole & 1100 mg sodium bicarbonate) capsules

Date of Application: March 10, 2008

Date of Receipt: March 10, 2008

Our Reference Number: NDA 22-281

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 9, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above must 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
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
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/cder/ddms/binders.htm.

If you have any questions, contact Geri Smith, Regulatory Project Manager, at geri.smith@fda.hhs.gov or (301) 796-2204.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
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/

Leah Christl
4/9/2008 04:24:35 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

SCHERING PLOUGH HEALTHCARE PRODUCTS INC
William Cochran
556 Morris Avenue S4-2, Mailstop 2180
Summit NJ 07901-1330
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22281

2. TELEPHONE NUMBER
908-4731858

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[ ] YES [X] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

21229

3. PRODUCT NAME
Zegerid OTC Capsules (Omeprazole/Sodium bicarbonate Capsules)

6. USER FEE I.D. NUMBER
PD3008090

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

OMB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
William Cochran	Sr. Manager, Regulatory Affairs	March 4, 2008

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$589,000.00

Form FDA 3397 (03/07)

Close Print Cover sheet

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 74,284

Schering-Plough HealthCare Products
Attention: John O'Mullane, Ph.D.
Group Vice President
556 Morris Avenue
Summit, NJ 07901-1330

Dear Dr. O'Mullane:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Zegerid (20mg omeprazole and sodium bicarbonate) capsule [redacted] b(4)

We also refer to your correspondence dated March 21, 2007 explaining how your development plan for Zegerid for OTC use will meet the fixed-combination drug requirements in 21 CFR 300.50.

We have completed the review of your submission and have the following comments.

1. We agree that the purpose of the sodium bicarbonate in your product is to enhance the absorption of omeprazole and will have no direct impact on providing heartburn symptom relief. To gain approval for Zegerid for the OTC treatment of frequent heartburn, you will need to provide a pharmacokinetic (pK) study that compares the bioavailability of your product to Prilosec OTC, the reference listed drug for the OTC indication. If the pK parameters fall outside of the bioequivalence criteria established by FDA for oral drugs, you will need to provide additional data to support the efficacy or safety of your product. This may require a clinical study depending what the difference entails. For example, if your product is less bioavailable than Prilosec OTC, you will have to provide clinical efficacy data to support the efficacy of your drug product.

2. If you are successful in bridging your product to Prilosec OTC through pK data, such data will not support a claim in labeling or advertising suggesting that your product is [redacted]. Additionally, labeling implying an [redacted] will not be acceptable based on such data. b(4)

3. The sodium bicarbonate is an active ingredient and should be listed in the active ingredient section of the Drug Facts label. Because it is not intended to have a direct impact on providing heartburn relief, the purpose should not be listed as [redacted] but as something such as "to assist in the absorption of omeprazole". b(4)

4. To assure that consumers will not be confused about the use of this product and the function of the sodium bicarbonate, you may be required to provide a label

comprehension study and possibly consumer behavior studies that demonstrate consumers will use the product correctly.

5. The product should contain sodium labeling if it falls within the criteria listed in 21 CFR 201.64.

6. Because consumers will be exposed to a daily dose of sodium bicarbonate, you will need to include any warnings that are applicable to sodium bicarbonate.

7. Because this product is a fixed-dose combination containing both omeprazole and sodium bicarbonate, it may present different safety issues when used OTC compared to single ingredient omeprazole. For example, the current labeling for prescription Zegerid includes contraindications in patients with metabolic alkalosis and hypocalcemia and cautions about use in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. These warnings are not applicable to single ingredient omeprazole. You will need to identify any potential safety issues included in the current prescription labeling or new safety issues after review of your safety database and determine how they should be addressed with OTC marketing. Despite being labeled for use for a fourteen day regimen, some people may use it longer than directed if it is available OTC. This should be factored into the considerations when attempting to address safety issues.

If you have any questions, call LCDR Keith Olin, Regulatory Project Manager, at 301-796-0962.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Office of Nonprescription Products
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/

Charles Ganley
7/18/2007 04:33:34 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 74,284

Schering-Plough HealthCare Products
Attention: William Cochran
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901-1330

Dear Mr. Cochran:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Zegerid OTC [redacted] capsule formulations. b(4)

We also refer to the meeting between representatives of your firm and the FDA on October 30, 2007. The purpose of the meeting was to discuss the proposed development program by SPHC in support of the Rx-to-OTC switch of [redacted] capsule formulations, specifically, [redacted] the proposed labeling for Zegerid OTC. b(4)

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LCDR Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION

Meeting Date and Time:	October 30, 2007
Meeting Type:	B
Meeting Category:	Pre-NDA
Application Number:	PIND 74,284
Product Name:	[redacted] b(4) Zegerid OTC (20mg omeprazole/sodium bicarbonate) capsules
Received Briefing Package	September 28, 2007
Sponsor Name:	Schering-Plough Healthcare Products
Meeting Requestor:	William Cochran
Meeting Chair:	Andrea Leonard-Segal, M.D.
Meeting Recorder:	Keith Olin, R.Ph.
FDA/CDER Attendees:	

Division of Nonprescription Clinical Evaluation

Christina Chang, M.D.	Medical Officer
Keith Olin, R.Ph.	Regulatory Project Manager
Joel Schiffenbauer, M.D.	Deputy Director
Andrea Leonard-Segal, M.D.	Director
Laura Shay, RN, MS, C-ANP	Social Science Analyst

Division of Gastroenterology Products

Hugo Gallo-Torres, M.D.	Medical Team Leader
Wen-Yi Gao, M.D.	Medical Officer

Division of Nonprescription Regulation Development

Reynold Tan	IDS Reviewer
Marina Chang, R.Ph.	Team Leader, IDS

OCP/Division of Clinical Pharmacology 3

Tien Mien Chen, Ph.D.	Pharmacology Reviewer
Sue Chih Lee, Ph.D.	Team Leader, Pharmacology

External Attendees:

Schering-Plough Healthcare Products

John O'Mullane, PhD	Group Vice President
Stephenie Barba	VP, Regulatory Affairs
Dennis Nelson, Ph.D.	VP, Research & Development OTC Medicines
Luis Salmun, MD	Senior Director, Medical and Scientific Affairs
Stephen Neumann	Senior Director Marketing Support Services
Gretchen Trout	Director, Regulatory Policy and Intelligence
Kristie Egstrand	Senior Rx to OTC Switch Marketing Manager
Ajmal Khan	Research Fellow
Bill Cochran	Manager, Regulatory Affairs
Nancy Miller-Rich	Vice President, Business Development
Kristie Egstand	Senior Business Development Marketing Manager Consultant
Thomas Blake	Regulatory Scientist

Santarus, Inc.

Warren E. Hall	Senior Vice President, Product Development and Manufacturing
E. David Ballard II, MD	Vice President, Clinical Research & Medical
Chares H. Davis	Senior Director, Regulatory Affairs

1.0 BACKGROUND

Schering-Plough Healthcare Products (SPHCP) submitted a meeting request to FDA on August 25, 2007 to discuss proposed labeling for their proposed Zegerid OTC formulations. The Zegerid capsule formulations were approved as prescription products under NDA 21-849 respectively, with Santarus, Inc. as the sponsor. SPHCP entered into an agreement with Santarus to develop the Zegerid products for OTC use. SPHCP intends to submit a new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the Zegerid products indicated for the nonprescription treatment of frequent heartburn (occurs 2 or more days per week) in adults 18 years of age and older.

b(4)

2.0 DISCUSSION

On October 29, 2007, FDA sent preliminary responses to SPHCP to address the questions in their September 28, 2007 meeting package. The questions from SPHCP appear below followed by the preliminary FDA responses in italics.

1 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

b(4)

Question 2:

Does the Agency concur that the data presented demonstrate that consumers do in fact understand the purpose of sodium bicarbonate in the formula and further that its presence does not deter from proper use of the product as directed? Further, does the Agency concur that no further label comprehension studies are needed?

FDA preliminary response:

A review of your label comprehension study results will be conducted when your NDA is submitted; whether or not additional label comprehension studies will be needed is ultimately a review issue.

Based on the summary of the study results you provided in the meeting background package, it is unclear why you are proposing to use the language b(4) *to describe the purpose of sodium bicarbonate (general population 63%, low literate population 56%). As stated in the July 18, 2007 Advice Letter, the "Purpose" section of Drug Facts should clearly describe the effect sodium bicarbonate has on omeprazole (e.g. "to assist in the absorption of omeprazole") and consumers should understand this purpose. In addition, the word ' may imply an added benefit. A targeted label comprehension study focusing on consumer understanding of the purpose of sodium bicarbonate for this product should be conducted.*

b(4)

We encourage you to submit your proposed study for our review and comment prior to initiating your study.

Question 3:

Does the Agency agree with the proposed labeling for Zegerid OTC with regard to the sodium bicarbonate content?

FDA preliminary response:

This will be a review issue when you submit your application.

The exact purpose of sodium bicarbonate in the label would depend on the result of an appropriately conducted label comprehension study.

You have not adequately addressed our labeling recommendations in Comment 7 of the July 18, 2007 Advice Letter. The warning statement "Ask a doctor before use if you have a sodium-restricted diet" does not adequately address our safety concern regarding bicarbonate-related metabolic disorders, nor does it address the prescription label's precaution regarding acid-base disorders. We do not agree that your proposed OTC warnings and directions statements communicate the same information as warnings in the current prescription labeling. As we stated in Comment 7, safety issues in the current prescription labeling need to be addressed in the OTC label. You should provide additional justification as to why you believe that some of the warnings from the prescription label are not needed in the OTC label.

Under "Ask a doctor or pharmacist before use if you are", you should include the following statements:

Presently taking any prescription drug(s) or taking any of the following:

Warfarin (blood-thinning medicine)

Prescription antifungal or anti-yeast medicines

Diazepam (anxiety medicine)

Digoxin (heart medicine)

Atazanavir (anti-viral medicine)

b(4)

b(4)

2.2 ADDITIONAL DISCUSSION

Schering-Plough Healthcare Products (SPHCP) opened the meeting by acknowledging the FDA preliminary comments sent to them. SPHCP noted that the PK data for the capsule is not available at this time but they committed to provide PK data for each Zegerid formulation compared with Prilosec OTC.

b(4)

b(4)

Next SPHCP asked FDA to clarify their preliminary response to Question 2. FDA reiterated that the data from the label comprehension study provided was not reviewed. Analysis of this data will only be conducted when the study is submitted in support of the new drug application. SPHCP acknowledged this. FDA stated that based on the summary results provided, SPHCP should conduct a targeted label comprehension study

that focuses on the new language describing the purpose of sodium bicarbonate and directions for use. SPHCP stated that they tested several terms to describe the purpose of sodium bicarbonate in their product, such as b(4)
but they would consider other terms.

. FDA suggested that SPHCP submit a protocol for FDA review and comment prior to conducting any study.

Regarding the preliminary response to Question 3, SPHCP asked why Zegerid should have additional labeled warnings addressing sodium bicarbonate-related metabolic disorders or acid-base disorders. SPHCP commented that AE's related to metabolic disorders were not seen in clinical trials and post-marketing reports and therefore they did not feel that wording related to metabolic disorders was needed. SPCHP also questioned the need for a sodium warning because there are products in the monograph with higher amounts of sodium that do not have all of these warnings. FDA suggested that SPHCP submit their rationale on why the sodium bicarbonate warnings should not be translated from the prescription Zegerid to the OTC formulations. FDA also recommended the same advice regarding the liver warning. SPHCP should include safety data concerning chronic exposure, including adverse events in individuals with liver and/ or kidney disease.

SPHCP commented that they will be including a statement in the label under the "Directions" section that the product should be taken before eating in the morning.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Neither FDA nor SPHCP identified any issues requiring further discussion.

4.0 ACTION ITEMS

1) SPHCP will provide a rationale to address the concern that differences in PK will translate into differences in efficacy when compared to Prilosec OTC. They will provide data to allow bridging of PK data to efficacy. SPHCP will submit this information to the FDA along with a request for a teleconference.

2) SPHCP will provide a rationale to the FDA addressing the warnings related to the Asian population.

3) SPHCP will provide a label comprehension study protocol to the FDA for review.

4) SPHCP will submit their rationale as to why the sodium bicarbonate warnings should not be translated from the Rx Zegerid to the OTC formulations.

5.0 ATTACHMENTS AND HANDOUTS

None

Linked Applications	Sponsor Name	Drug Name
IND 74284	SCHERING-PLOUGH HEAL	ZEGERID IR

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

/s/

KEITH J OLIN
11/29/2007

ANDREA LEONARD SEGAL
11/29/2007

Telecon Minutes Memo

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products

Date: 4-25-07

Participants: John O'Mullane, Ph.D., Schering-Plough HealthCare Products
Charles Ganley, M.D.

Discussion Issues: Clinical requirements for Zegerid (PIND #74-284); information amendment dated

- We met with John Jenkins and the lawyers from CDER Office of Regulatory Policy and FDA Office of Chief Counsel.
- There is a letter in draft that probably will not be cleared for another month.
- The preliminary decision is:
    - A bridging pharmacokinetic study would suffice if bioequivalence criteria are met. If the bioequivalence criteria are not met, they would have to provide additional information to support the efficacy and/or safety. This may include additional clinical studies depending on what the data shows.
    - Sodium bicarbonate is an active ingredient but the purpose is not as an antacid. It would be described something such as "adjuvant to assist the absorption of omeprazole".
    - There are several other caveats alluded to but not discussed.

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

/s/

Charles Ganley
5/2/2007 12:07:50 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 74,284

Schering-Plough HealthCare Products
Attention: William Cochran
Manager, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901-1330

Dear Mr. Cochran:

b(4)

Please refer to your Pre-Investigational New Drug Application (PIND) file for Zegerid capsule formulations.

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2007. The purpose of the meeting was to discuss the proposed development program by Schering-Plough HealthCare Products (SPHC) in support of the Rx-to-OTC switch of Zegerid capsule formulations, specifically, that the comparative bioavailability study meets the criteria for approval and to gain agreement on the elements and design of the labeling for Zegerid.

b(4)

The official minutes of that meeting were signed off by the FDA on March 9, 2007. At the time of the meeting, there was an outstanding item that required follow-up by SPHC to submitted additional chemistry stability data. SPHC felt that there was an agreement in regards to the chemistry stability data which was discussed at the meeting on October 26, 2005. SPHC submitted the requested information as an amendment on March 10, 2007.

Enclosed is a revised copy of the March 9, 2007 meeting minutes edited to correct minor typographical errors and to include a post-meeting addendum to the minutes addressing the outstanding issue described above in reference to Question 3.

This letter and the enclosed meeting minutes represent the official record of the meeting on February 7, 2007.

If you have any questions, call LCDR Keith Olin Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Director
Division on Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

FOOD AND DRUG ADMINISTRATION

Meeting Date:	February 7, 2007
Meeting Type:	B
Meeting Category:	pre-IND
Meeting Location:	FDA/White Oak 10903 New Hampshire Ave Room 1415 Silver Spring, MD 20993
Application Number:	PIND 74,284
Product Name:	/ ✓ b(4) Zegerid omeprazole/sodium bicarbonate immediate release capsules
Received Briefing Package	January 8, 2007
Sponsor Name:	Schering-Plough Healthcare Products
Meeting Requestor:	William Cochran Manager, Regulatory Affairs
Meeting Chair:	Andrea Leonard-Segal, M.D., Director
Meeting Recorders:	Keith Olin, R.Ph., Regulatory Project Manager

FDA/CDER Attendees:

Office of Nonprescription Products (ONP)

Charles Ganley, M.D.	Director

ONP/Division of Nonprescription Clinical Evaluation

Leah Christl, Ph.D.	Chief, Project Management Staff
Wafa Harrouk, Ph.D.	Pharmacology/Toxicology Reviewer
Andrea Leonard-Segal, M.D.	Director
Bindi Nikhar, M.D.	Medical Team Leader
Keith Olin, R.Ph.	Regulatory Project Manager
Linda Hu, M.D.	Medical Officer
Joel Schiffenbauer, M.D.	Deputy Director
Daiva Shetty, M.D.	Medical Team Leader

ONP/Division of Nonprescription Regulation Development

Helen Cothran	IDS Team Leader
Reynold Tan, Ph.D.	IDS Reviewer

Division of Gastroenterology Products

Joyce Korvick, M.D.	Deputy Director
Ruyi He, M.D.	Medical Team Leader
Nancy Snow, M.D.	Medical Officer
Michael Welch, Ph.D.	Statistician Team Leader

Division of Clinical Pharmacology 2

Suresh Doddapaneni, Ph.D.	Team Leader, Clinical Pharmacology
Lei K. Zhang	Senior Staff Fellow

Division of Pre-Marketing Assessment II

Shulin Ding, Ph.D.	Lead Chemist

Division of Pharmcology III
Tien-Mien Chen, Ph.D.

External Attendees:

Schering-Plough Healthcare Products

John O'Mullane, PhD	Group Vice President
Luis Salmun, MD	Senior Director, Medical and Scientific Affairs
Robert Nowak, PhD	Director, Clinical Research
Ajmal Khan	Research Fellow
Bill Cochran	Manager, Regulatory Affairs
Nancy Miller-rich	Vice President, Business Development
Kristie Egstand	Senior Business Development Marketing Manager Consultant
Thomas Blake	Regulatory Scientist

Santarus, Inc.

Warren E. Hall	Senior Vice President, Product Development and Manufacturing
E. David Ballard II, MD	Vice President, Clinical Research & Medical

1.0 BACKGROUND

Schering-Plough HealthCare Products (SPHC) submitted a pre-IND meeting request on November 22, 2006, received on November 27, 2006, to discuss a regulatory approach for an prescription-to-over-the-counter (Rx-to-OTC) switch for Zegerid [redacted] capsule formulations. The Zegerid [redacted] capsule formulations were approved as prescription products under [redacted] NDA 21849 respectively, with Santarus, Inc. as the sponsor. SPHC entered into an agreement with Santarus to develop the Zegerid products for OTC use. According to the January 5, 2007 meeting package, SPHC intends to submit a new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the [redacted] Zegerid products indicated for the treatment of frequent heartburn (occurs 2 or more days per week) in adults 18 years of age and older. b(4)

FDA met with Santarus, Inc. on October 26, 2005 to discuss the Rx-to-OTC switch of Zegerid [redacted] capsule, [redacted] The meeting minutes for the October 26, 2005 between Santarus and the FDA were issued on November 22, 2005. During the meeting on October 26, 2005, the issue of the applicability of the combination policy for Zegerid as a OTC drug product as per 21 CFR 330.10, subpart B(4)(iv) was not address but a response to this was issued on January 30, 2007. It was determined that the Zegerid products contain two active ingredients, omeprazole and sodium bicarbonate, each of which are available in nonprescription drug products for heartburn indications. Santarus was informed that they would have to satisfy the combination policy by conducting two clinical superiority studies that demonstrate the efficacy and safety of the Zegerid products as nonprescription products to treat frequent heartburn. b(4)

Prior to the February 8, 2007 meeting, FDA verified that Santarus had shared the FDA's comments and recommendation with SPHC.

2.0 MEETING OBJECTIVE

The objective of the meeting was to discuss the proposed development program by SPHC in support of the Rx-to-OTC switch of Zegerid [redacted] capsule formulations, specifically, that the comparative bioavailability study meets the criteria for approval and to gain agreement on the elements and design of the labeling for Zegerid. (b)(4)

3.0 DISCUSSION

Preliminary responses to the questions enclosed in the January 5, 2007, meeting package were sent to SPHC via e-mail on February 6, 2007. These questions and preliminary FDA responses are listed below.

Following introductions, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA.

3.1 FDA Preliminary Responses

3.1.1 Chemistry

The Chemistry, Manufacturing and Controls for the OTC forms of Zegerid®, omeprazole/sodium bicarbonate [redacted] (omeprazole 20 mg) will be virtually identical to those for the prescription products, with the slight exception that tamper evident banding will be applied to the capsules, as per 21 CFR 211.132. Thus, Schering-Plough will reference the currently approved NDAs for Zegerid, including existing stability and expiry dating, in its application for the OTC version. b(4)

[redacted] b(4)

20 mg Capsule

The following changes to the capsule are anticipated to accommodate the OTC indication (see Exhibit 8.2.1 for more details):

The capsule shell will be all white (Deletion of FD&C Blue #1 and FD&C Red #3 in the capsule shell) as opposed to the half blue/half white color of the Rx product. The capsule imprint graphic will change but the qualitative composition of the imprinting ink will not. A tamper evident band ([redacted] Gelatin using same FD&C Blue #1 dye as is found in the Rx capsule shell) will be added to the capsule as per the requirements of 21 CFR 211.132. The tamper evident band is on the outside of the capsule shell and will not be in contact with the capsule contents. b(4)

A tamper evident feature will also be added to the bottles.

2. We intend to use the current Rx marketed product (blue/white capsule without tamper evident band) in the proposed comparative bioavailability study for the 20 mg capsule product? We plan to demonstrate that the banded capsule meets the current approved dissolution specification for the unbanded capsule. Does the Agency agree with this approach?

FDA Preliminary Response:
The approach appears acceptable provided that 1) virtually, no changes are made to omeprazole drug substance and/or no higher than level 1 changes to the manufacturing site/processes of the proposed omeprazole OTC IR 20 mg capsules other than for coloring agents and packaging of the final OTC IR 20 mg products and 2) dissolution testing meets the currently approved dissolution specification and shows similar dissolution profiles between the currently marketed Zegerid 20 mg IR capsules and the proposed OTC omeprazole IR 20 mg capsules.

3. Schering-Plough will commit to placing the first three commercial lots of 20 mg OTC capsules on stability post-approval (as will be outlined in the stability commitment submitted in the OTC NDA). Would the Agency agree that the changes bulleted above to the capsule would not require generation of pre-market stability data based on full cross-reference being granted to the Rx NDA and stability data contained therein. Would the Agency agree that the OTC NDAs (with changes as summarized above) could be granted approval of the Rx approved expiry dating based on the aforementioned proposal?

FDA Preliminary Response:
No, we disagree. Pre-market stability data will be required for the OTC NDAs on capsules because of the changes outlined on page 49 of the briefing package. The actual expiry period granted is a review issue.

3.1.2 Clinical/Safety Evaluation

4. Schering-Plough proposes to submit New Drug Applications under the provisions of section 505(b)(2) of the Food, Drug, and Cosmetic Act for the OTC marketing of Zegerid, omeprazole/sodium bicarbonate (omeprazole 20 mg) in Capsule. The prescription equivalents were approved by the Agency in 21-849 (Capsule), sponsored by Santarus, Inc. of San Diego, CA. Using a comparative bioavailability study, discussed below, Schering-Plough proposes to compare Zegerid, omeprazole 20 mg and sodium bicarbonate, with Prilosec OTC 20mg (NDA 21-229). Accordingly, Schering- Plough intends to rely on the Agency's findings of safety, efficacy, and approvability for Prilosec OTC in order to support the NDA submission for Zegerid. Does the Agency agree that a 505(b)(2) application, supported by the data from the comparative bioavailability study outlined in Question 2 fulfills the requirements for approval? b(4)

FDA Preliminary Response:
A comparative bioavailability study would support a 505(b)(2) application, but additional data are needed (see below).

5. Schering-Plough's proposal for equivalence of each of the Zegerid dosage forms with Prilosec OTC will be based on a single dose pharmacokinetic study as per the attached protocol synopses (See Exhibits 8.1.1 and 8.1.2). The primary outcome measure will be bioequivalence to Prilosec OTC with respect to AUC. From a safety standpoint, FDA relied upon AUC when it approved Prilosec OTC tablets, since the drug's Cmax was shown to be significantly higher than that for Prilosec Capsules, the prescription form of the drug. The relevant portion of the Summary Basis of Approval (SBA) for Prilosec OTC (NDA 21-299) is attached for reference (See Exhibit 8.1.3). Also, the single dose design is the basis by which the Office of Generic Drugs evaluates bioequivalence for the generic forms of omeprazole 20mg, as illustrated by a description of the Study No. 97273 in the SBA for ANDA 75-247 Is the Agency in agreement with this approach? b(4)

FDA Preliminary Response:
It should be noted that the word, "bioequivalence (BE)", is reserved only when the Agency's acceptance criteria for BE are met, i.e., the 90% confidence intervals of the ratio of least-square means for both $AUC_{(0\text{-}inf)}$ and C_{max} fall within 80-125%. Therefore, as stated in the proposed protocols, 90% confidence intervals should be calculated for the ratio of least-square means for both $AUC_{(0\text{-}inf)}$ and C_{max} of currently marketed Zegerid to omeprazole OTC 20 mg capsules.

In addition, it should be noted that post-marketing safety data, clinical trial safety and efficacy data and consumer study data were also submitted to support the Prilosec OTC switch. It would be erroneous to suggest that the safety of Prilosec OTC was based only on a pharmacokinetic comparison to the prescription omeprazole product.

Observed differences in the bioavailability of Zegerid and Prilosec OTC would need to be justified or supported by appropriate safety and/or efficacy data. If Zegerid is more bioavailable than Prilosec OTC, more safety information would be needed. If your product is less bioavailable, efficacy data would be needed.

Your product contains two active ingredients, omeprazole and sodium bicarbonate. Omeprazole magnesium is an approved nonprescription drug to treat heartburn and sodium bicarbonate a nonprescription ingredient generally recognized as safe and effective to relieve heartburn. Therefore, even if the omeprazole component of your product proves to be bioequivalent to Prilosec OTC this will be insufficient to support the prescription to OTC switch of Zegerid. You will need to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv). This may be achieved by conducting two clinical studies that demonstrate the contribution of each active ingredient to the efficacy of Zegerid to treat frequent heartburn.

6. Since Zegerid, like Prilosec OTC, will be taken on an empty stomach, the studies will be conducted in the fasting state only. Is the Agency in agreement with this approach?

FDA Preliminary Response:
The approach appears acceptable.

7. The Agency did not require or recommend additional safety studies as a condition for approval of the Zegerid 20 mg Rx NDAs'. As these NDAs were 505(b)(2) applications, Santarus referenced several NDAs for omeprazole, particularly those for Prilosec (NDA 19-810) for the safety portions. Does the Agency agree that no additional safety studies will be required for Zegerid, omeprazole/sodium bicarbonate [redacted] (omeprazole 20 mg) if, 1) its bioavailability profile is comparable to that of Prilosec OTC (omeprazole 20 mg), especially with respect to AUC, or 2) if Zegerid's profile is unexpectedly higher, that concerns about safety are adequately addressed by the safety database for omeprazole 40 mg, the highest strength of the prescription drug? b(4)

FDA Preliminary Response:
If Zegerid is not bioequivalent to Prilosec OTC, but its PK profile is unexpectedly higher (for example, higher Cmax), then additional safety data would be needed. Omeprazole 40 mg is not approved for OTC use.

3.1.3 Regulatory/Procedural

The sponsor of the NDAs for the prescription forms of Zegerid, Santarus granted Schering-Plough a full right of reference to its NDAs in order to facilitate our program for gaining OTC status for the drug.

8. Schering-Plough plans to submit the comparative bioavailability study information to the newly created file, IND 74,284, with appropriate references to the INDs and NDAs for the currently approved Zegerid products. Since the single dose of Zegerid 20mg to be given in the comparative bioavailability study falls well within the drug's margin of safety and is covered by its approved labeling. Please confirm that the standard 30-day IND hold will not apply.

FDA Preliminary Response:
The standard 30-day IND hold would not apply if you can provide evidence that this product is the same as the approved prescription Zegerid product.

3.1.4 Labeling

9

b(4)

10. In view of Prilosec OTC's marketing history and the information in its NDA, does FDA agree that additional labeling comprehension and actual use studies are unnecessary?

FDA Preliminary Response:
Since your product contains two active ingredients, omeprazole and sodium bicarbonate, each of which is an approved nonprescription drug for heartburn, additional clinical studies that demonstrate the contribution of each ingredient to the efficacy of Zegerid to treat frequent heartburn are needed. Final labeling will depend on the results of these trials. If the labeling is substantially different from that of Prilosec OTC, then consumer comprehension (and/or behavior studies) may be needed. It is premature to discuss whether additional label comprehension and actual use trials are needed at this time.

3.1.5 Additional Comment:

Each 14 day course of your product should be packaged separately to further emphasize that 14 tablets constitute one course of therapy to treat frequent heartburn.

3.1.6 Additional Administrative Comments:

Comments shared today with you are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate the meeting discussion. As this meeting is a Pre-IND meeting, the comments from the Agency serve as guidance to you at

this preliminary stage. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the IND might identify additional comments or informational requests.

For applications submitted after February 2, 1999, applicants are required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

We remind you of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We encourage you to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on Phase 1 and Phase 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

Your pre-IND has been assigned 74,284. Please reference this number on all submissions and correspondence. Please note, studies in humans may not be conducted under this PIND. Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312).

When you submit you Investigational New Drug Application, please provide 6 copies.

3.2 Additional Discussion

SPHC opened the meeting with a review of the history of the development of the Zegerid products as prescription products and provided an argument to support why they should not have to conduct clinical trials for their proposed OTC products. The Division of Gastrointestinal Drug Products reviewed data for the prescription application that they felt fulfilled the combination policy for the indication being sought.

FDA responded that for the OTC indication, there are several other factors in the regulatory history that are important when determining what studies may be needed to support an OTC indication of frequent heartburn. They are as follows:

- Sodium bicarbonate is an active ingredient in the OTC drug monograph for the indication of relief of heartburn. From a regulatory perspective, it is no less of an active ingredient than an H2 blocker for this claim.
- In the past, FDA determined that the combination of an antacid and H2 blocker was acceptable for a claim of relief of heartburn. Companies would have to demonstrate

the contribution of each ingredient. For the combination of famotidine and an antacid, the sponsor was required to conduct clinical studies that demonstrated the contribution of each ingredient. b(4)

- FDA can not view sodium bicarbonate any differently than other active ingredients for heartburn relief, such as famotidine or ranitidine. So, if a company wanted to come in for a combination of an H2 blocker and omeprazole, FDA would expect them to fulfill the combination policy and conduct clinical trials that demonstrate the contribution of each ingredient.
- If FDA allowed a claim for frequent heartburn Zegerid without conducting clinical trials, b(4)

  When Prilosec OTC was being developed, multiple studies were conducted to evaluate the effect for the relief of heartburn. None of these studies demonstrated a benefit. If however, omeprazole was combined with an antacid, it may be possible to show a treatment effect in part because of the antacid. FDA has to be consistent with how it deals with combinations such as that proposed for all of the OTC heartburn indications.
- b(4)

FDA reiterated to SPHC that the Zegerid formulation is a combination product and will have to follow the combination policy. The FDA stated that they understood that SPHC is using the sodium bicarbonate to protect the omeprazole from stomach acid degradation. If they combined an H2 blocker with omeprazole instead of the antacid, we would expect them to fulfill the combination policy and conduct two clinical studies. FDA explained that there is a regulatory history that needs to be considered and that SPHC's formulation can be compared to other products on the market like a famotidine and antacid combination, which was required to follow the combination policy by demonstrating the contribution of each ingredient. FDA determines what types of trials would be acceptable.

SPHC stated that they agree that the product is a combination drug, but that they felt that they were being held to a different standard with trying to switch the Zegerid product to the OTC marketplace. FDA explained that the reviewing divisions within the Office of New Drugs what information is needed to fulfill the combination policy which is based on different factors such as the indication, the class of drug and previous regulatory precedent. The review divisions have the discretion of deciding what information may be needed for the required studies to comply with the combination policy.

FDA stated that it understands that the sodium bicarbonate is included in Zegerid because of formulation issues, but explained that SPHC has the option of reformulating, as others have done, instead of combining another active ingredient to take care of the problem. FDA explained that the difficulty here is that SPHC is seeking a heartburn indication by combining two drugs that have heartburn indications on their own. In addition, FDA has permitted combinations of two different drugs to treat heartburn, one of them an antacid, and required that the clinical contribution of each ingredient be established through clinical studies.

SPHC noted that if they conducted a factorial study with their product, the individual components and placebo, that the arm with "naked" omeprazole would show no benefit because it would be destroyed by stomach acid. SPHC was told they would likely have to include an omeprazole formulation that demonstrated a clinical benefit superior than placebo. FDA stated that they generally do not accept a factorial study as valid if one of the single ingredient active arms includes a formulation of an active ingredient that is not effective. Also, this combination would also raise issues about whether it is rational to combine these ingredients for a frequent heartburn indication. In the past, FDA determined that the combination of an antacid and an H2 blocker was not rational for a prevention of meal induced heartburn claim. FDA stated that SPHC would need to provide support that this formulation is a rational combination for the indication sought. FDA stated that they had concerns regarding chronic use of omeprazole that SPHC would also have to address.

With regard to relying on the safety database for omeprazole 40 mg to support the safety of the Zegerid products (refer to Question 7), FDA explained that SPHC could provide the safety data from their current 40 mg prescription omeprazole product but that SPHC would need to compare and contrast the data with omeprazole 20 mg.

FDA encouraged SPHC to provide a written response to FDA outlining their argument as to why their product should not be required to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv) with clinical studies. FDA stated that they would expedite a response to SPHC.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

SPHC/Santarus felt that an agreement to question 3 in regards to submitting the stability data was made at the first meeting in October 26, 2005 when Santarus met with the FDA and that the response that FDA provided for the February 8, 2007 meeting was different than the meeting minutes from the October 2005 meeting. Below is the response by the FDA given at the October 2005 meeting:

(October 2005) Question 5.
Does the Agency agree that Santarus can rely on the stability data generated for Zegerid 20-mg Rx capsules (packaged in bottles of 5 and 30) to support Zegerid OTC 20-mg

capsules (packaged in identical bottles of 14 and 28) and therefore, no additional stability studies are required?

FDA Response:

This proposal appears to be acceptable. See response to Question 6 below. It should be noted that NDA 21-849 is still under review.

b(4)

b(4)

5.0 ACTION ITEMS

1. SPHC will provide the FDA with a written response about why their product should not be required to satisfy the combination policy for OTC drug products as per 21 CFR 330.10 subpart B(4)(iv).
2. FDA agreed to expedite the review SPHC's response.
3. FDA will follow-up on the stability issue and possible agreement made in October 2005.

6.0 ATTACHMENTS AND HANDOUTS

None

7.0 POST_MEETING ADDENDUM

SPHC submitted an amendment to their meeting package on March 10, 2007 that included the data that the FDA requested at the February 7, 2007 meeting. The submission included a summary of the bracketing approach for package sizes from 5 capsules to 30 capsules and a table summarizing the bottle dimensions, including headspace.

The FDA agrees with SPHC's proposal submitted on March 10, 2007, for the additional supporting chemistry data regarding headspace, surface area, and volume for the bottles used in the prescription NDA and the proposed OTC product. The FDA also agrees that the information provided in the amendment shows that the OTC packaging configurations of 14 and 28 counts are bracket by the approved prescription configurations of 5 and 30 counts. This information should be included in any NDA submission as justification.

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

/s/

Andrea Segal
5/1/2007 11:25:47 AM