CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021019

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

SmithKline Beecham
Pharmaceuticals

March 3, 1999

NDA 21-019
Compazine® (prochlorperazine maleate)
Spansule® Capsules
Pages 000001-000006

Russell Katz, M.D., Acting Director
Division of Neuropharmacological
Drug Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: Response to Request for Information

Dear Dr. Katz:

Reference is made to our new drug application of September 29, 1997 for Compazine® (prochlorperazine maleate) Spansule® Capsules, NDA 21-019, which describes reformulation of the drug product as a replacement for the current [illegible] Compazine® Spansule® product, and changes the drug product manufacturing site from the SB Spring Garden Street facility, Philadelphia, PA to International Processing Center (IPC), Winchester, KY, with packaging to be performed at [redacted].

Additional reference is made to a telephone conversation held on March 2, 1999 between Lisa Marie Reed (SB) and Merril Mille (FDA) wherein it was requested that SB provide any relevant patent information for this product. Please note that SB does not intend to declare specific patent information at this time for the reformulated Compazine® Spansule® capsules.

Additionally it was requested that we provide a debarment certification for Bioequivalence Study 011, "A Single Dose Study to Determine the Bioequivalence of Two Sustained Release Formulations of Prochlorperazine Maleate and Compazine Spansules in Healthy Volunteers" (SB Document No. SKF-004657/RSD-100).

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

NDA 21-019
Compazine® (prochlorperazine maleate)
Spansule® Capsules

Submitted herein is the requested debarment certification per 306(k)(1) of the Federal Food, Drug and Cosmetic Act.

If you have any questions about this information, please feel free to contact me at (610) 917-7723.

Sincerely,

Peter J. Kitz
Group Director
Worldwide Manufacturing Support
Chemistry Manufacturing and Supply

Desk Copy: Anna Marie Hommonay-Weikel (hard copy)
Merril Mille (facsimile and hard copy)

COPY

Signed: 3/12/99

EXCLUSIVITY SUMMARY FORM

(Modified: October 14, 1998)

Exclusivity Summary FOR NDA # 21-019 SUPPL #_____

Trade Name: Compazine Generic Name: prochlorperazine maleate

Applicant Name: Smithkline Beecham Pharmaceuticals HFD # 120

Approval Date If Known:_____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

   If yes, what type? (SE1, SE2, etc.) _____

   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 / X /

   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.

   Study Report #11 titled: "A Single Dose Study to Determine the Bioequivalence of Two Sustained Release Formulations of Prochlorperazine Maleate and Compazine Spansules in Healthy Volunteers"

   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 / X /

   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 /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /_X_/ NO /____/

If yes, NDA # 11-000__ Drug Name Compazine Spansule Capsules

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 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# _____ _____

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# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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:

Investigation #1, Study # _____
Investigation #2, Study # _____
Investigation #3, Study # _____

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:

NDA # _____ _____
NDA # _____ _____

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:
NDA # _____ _____
NDA # _____ _____

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"):
NDA # _____ _____
NDA # _____ _____

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 /___/ Explain _____ NO /___/ Explain _____
_____ _____

Investigation #2
YES /___/ Explain _____ NO /___/ Explain _____
_____ _____

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

YES /___/ NO /___/

If yes, explain: _____
_____
_____

/S/ 3/1/99
Signature Date
Regulatory Management Officer

/S/ 3/12/99
Signature of Office/Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac
Typed: 12/02/98

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21019	**Trade Name:**	COMPAZINE(PROCHLORPERAZINE)SPANSULE CAPS
Supplement Number:		**Generic Name:**	PROCHLORPERAZINE MALEATE CAPS 10/15MG
Supplement Type:		**Dosage Form:**	CRC
Regulatory Action:	AE	**Proposed Indication:**	For control of severe nausea and vomiting. Management of the manifestations of pschotic disorders. short-term tx of generalized non-psychotic anxiety

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ✓ Children (25 Months-12 years)
____Infants (1-24 Months) ✓ Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
3-1-99: new formulation; no new clinical data. 14-SEP-99: no patent declaration; no exclusivity request

pediatric dosage recommendations approved under NDA 11-000

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MERRIL MILLE

/S/

Signature

15-SEP-99

Date

reviewed by TL
9-15-99

NDA 21-019

Compazine® (prochlorperazine maleate) Spansule® Capsules

Item 16. Debarment Certification

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

Mike

MEMORANDUM

DATE: March 8, 1999

FROM: Acting Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-019

SUBJECT: ~~Approval~~ AE Action for NDA 21-019 for Compazine Spansule Capsules

On 9/29/97, SmithKline Beecham submitted a supplement to their NDA 11-000 for Compazine Spansules (10 and 15 mg) for a reformulated capsule. This reformulated capsule contained an entirely different mechanism for drug release than that incorporated in the current product. Because of this major change, the supplement was subsequently re-assigned as NDA 21-019 (see letter of 6/18/98). As support for this reformulation, the sponsor submitted CMC data, as well as a 3 arm bioequivalence study comparing a single 30 mg dose given as 3X10 of the current and 2 different proposed 10 mg capsules.

This submission was reviewed by Dr. Baweja of OCPB, (review signed 10/9/98) and by Dr. Ramsharan D. Mittal, chemist, HFD-110 (review dated 12/30/97). Dr. Mittal found several minor deficiencies, but Dr. Baweja concluded that, while bioequivalence had been established for one of the proposed formulations, the other formulation was not equivalent to the marketed spansule. Further, he recommended that multiple dose data be submitted to examine steady state Cmin of the new product, given the major change in formulation being proposed. In addition, he felt that a study of the effects of food on the performance of the product should be performed.

A Not Approvable letter was issued on 2/19/98. The reason stated in the letter was that the new formulation was not bioequivalent to the marketed spansule because of a failure of Cmax to meet the acceptance criteria (the reasoning is unclear to me, given that the specific formulation proposed by the sponsor as the one that they wished to market was shown to be equivalent to the marketed capsule).

In any event, the sponsor responded in a submission dated 5/4/98, and a second Not Approvable letter issued on 10/28/98. In this letter, Dr. Baweja's comments were cited as the reasons for the action; that is, there was no multiple dose study, and a food study had not been submitted.

A second review by Dr. Baweja, signed 2/16/99, reviews submissions dated 11/24/98, 12/23/98, and 1/12/99. In the 11/24/98 submission, the sponsor argued that a steady state study in normals was not feasible. As a result, Dr. Baweja had agreed that steady state simulations for the 15 mg tablet would be adequate to assess the Cmins of the 2 products (his primary concern about utility of the new product at steady state), and the results of such a simulation were submitted, as were the results of a study comparing the kinetics of the new spansule in the fed and fasted state.

In this review, Dr. Baweja notes that the Cmin of the new product at steady state was about 15% lower than that of the marketed product (1.1ng.ml vs 1.3 ng/ml), but that the new product was less variable than the marketed product. Further, in the food study, the Cmax of the new spansule in the fed state was about 25% lower than that of the new spansule in the fasted state (1.12 ng/ml vs 1.46 ng/ml).

Finally, additional CMC reviews have been performed by Dr. Lostritto of ONDC (reviews dated 10/25/98 and 2/22/99). In the latter review, Dr. Lostritto recommends that the application be approved.

COMMENTS

The sponsor has demonstrated bioequivalence of the proposed 10 mg spansule to the marketed 10 mg spansule in a single dose study. The kinetics of the product at steady state have been evaluated by simulations. In addition, the effects of food on the performance of the proposed product have been assessed.

The Cmin of the new product is slightly lower than that of the marketed product at steady state. While strict bioequivalence criteria cannot be applied to this simulated finding, it is reasonable to permit this finding to stand, given that the use of this drug chronically is unusual (as discussed by Dr. Baweja in his second review, and as noted by Dr. Laughren, Psychiatric Drugs Team Leader in a personal conversation, Compazine is rarely used to treat schizophrenia, despite its having such an approved indication).

The effect of food, however, would appear to be of concern, given that the Cmax is about 25% less than what it is in the fasted state, and the bioequivalence of the product was based on a fasted comparison of the new and old spansules. That is, the effectiveness of the product when given with food can be questioned, given that the Cmax may be critical for effectiveness when the drug is given acutely. Bioequivalence criteria have not been applied to this parameter, and no information about the performance of the marketed product when given with food is presented.

I am not overly concerned, however, given that the product is given to patients who are severely nauseated or vomiting, in whom food consumption is likely not to be an issue, especially after an initial acute dose.

RECOMMENDATIONS

Both Drs. Baweja and Lostritto recommend that the application can be approved with several minor labeling changes. Dr. Baweja also recommends that the sponsor adopt specific dissolution specifications.

I agree that the application is approvable. As such, I will sign the attached Approvable letter which describes the labeling changes recommended above and the dissolution specifications proposed by Dr. Baweja.

/S/

Russell Katz, M.D.

Cc:
NDA 21-019
HFD-120
HFD-120/Katz/Laughren/Lostritto/Mille
HFD-860/Baweja

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: October 4, 1999

/S/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Compazine (prochlorperazine maleate) Spansule Capsules (10 and 15 mg)

TO: File NDA 21-019
[Note: This memo should be filed with the 4-27-99 re-submission.]

The complicated history of this NDA up to the issuance of 3-9-99 approvable letter is reviewed in a 3-8-99 memo to the file by Dr. Katz. Briefly, this NDA involves a reformulated sustained release capsule for Compazine as well as a site change for its manufacture. Because of the substantially different release mechanism for the new formulation, a single dose bioequivalence study was deemed unacceptable. As a result, there were 2 not approvable letters (2-19-98 and 10-28-98). We subsequently reached agreement with the sponsor that steady state simulations would be acceptable along with a food effect study, and these data were submitted, reviewed, and considered to have been largely acceptable. In fact, the issues included in the 3-9-99 approvable letter were relatively minor, i.e., requested language describing the food effect in labeling, a modification of the storage statement in labeling, and revised dissolution specifications.

However, the sponsor, in its 4-27-99 response, disputed the food effect language for labeling and the revised dissolution specs. Dr. Baweja from OCPB argued that our original proposals on these issues should be accepted (see 8-16-99 review). Through negotiation, the remaining differences were resolved, and we have reached agreement on both the exact language for the food effect statement and dissolution specifications. Regarding food effect, the sponsor has agreed in a 9-21-99 fax to accept our proposed language. Regarding dissolution, the sponsor has agreed in a 9-28-99 fax to accept

The other CMC issues in the 4-27-99 response were minor, i.e., storage statement and container label, and the CMC group has recommended approval of this application (see 9-23-99 review).

In conclusion, I agree that this NDA can now finally be approved, and I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 21-046
HFD-120/DivFile
HFD-120/TLaughren/RKatz/MMille

DOC: NDA21019.01

Homonnay

NDA 21-019

JAN 27 1999

SmithKline Beecham Pharmaceuticals
Attention: Peter Kitz
1250 South Collegeville Rd.
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Mr. Kitz:

We acknowledge receipt on January 13, 1999, of your January 12, 1999, resubmission to your new drug application (NDA) for COMPAZINE (prochlorperazine maleate) SPANSULE capsules which provides for reformulation of the drug product and changes to the drug product manufacturing site.

This resubmission contains additional information submitted in response to our October 28, 1998, action letter. We also refer to our January 11, 1999, teleconference during which additional pharmacokinetic computer simulations for 12 hour dosing were requested by FDA.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is March 13, 1999, and the secondary user fee goal date is May 13, 1999.

If you have any questions, contact Anna Marie Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely,

/S/

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

MEMORANDUM OF TELECON

DATE: 1/11/99

NDA: 21-019

DRUG: Compazine[R] Spansules[R]

BETWEEN:

SmithKline Beecham(SB)
Steve Boike
Marty Hyneck
David Tenero
Peter Kitz
Dale Stockbower
David Wheadon
Susan Milosovich

APPEARS THIS WAY
ON ORIGINAL

AND:

FDA
Dr. Mehta (HFD-860)
Dr. Baweja (HFD-860)
Anna M. Homonnay-Weikel (HFD-120)

SUBJECT: Bioequivalence requirements for reformulation and site transfer of Compazine[R] Spansules[R]

BACKGROUND: FDA requested the teleconference after receipt of the December 23, 1998, amendment containing the requested computer simulation data. The purpose of the teleconference was to request additional computer simulation data.

APPEARS THIS WAY
ON ORIGINAL

DISCUSSION:

- Dr. Baweja indicated that FDA would like to see further computer simulated data involving steady state levels resulting from Q12 hour dosing of COMPAZINE to correspond with the product labeling.

- SKB agreed to provide this data as soon as possible, by the end of this week.

/S/

Anna M. Homonnay-Weikel, R.Ph.
Project Manager

cc:
Orig NDA
Div File
HFD-120/Laughren/Dubitsky
HFD-120/Homonnay

C:\WPFILES\NDA\COMPAZIN\21019.TC2

TELECONFERENCE

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: 12/21/98

NDA: 21-019

DRUG: Compazine™ Spansules™

BETWEEN:

SmithKline Beecham(SB)
Steve Boike
Marty Hyneck
David Tenero
Peter Kitz
Dale Stockbower
David Wheadon
Susan Milosovich

AND:

FDA
Dr. Mehta (HFD-860)
Dr. Baweja (HFD-860)
Anna M. Homonnay-Weikel

SUBJECT: Bioequivalence requirements for reformulation and site transfer of Compazine Spansules

BACKGROUND: SB requested the teleconference after receipt of a second not approvable letter on October 28, 1998, requesting more in vivo bioequivalence data. The purpose of the teleconference was to provide further guidance to SB for the unresolved bioequivalence issues. The December 14, 1998, correspondence they submitted containing several proposals served as the basis for the ensuing discussion.

DISCUSSION:

- The SB dissolution proposal, as set forth in the December 14, 1998, correspondence is considered adequate.

- The response in the December 14, 1998, correspondence concerning the food effect study is acceptable.

- The Division is prepared to accept computer simulation results between test and reference products at the end of the dosing interval in lieu of conducting a multi-dose bioequivalence study due to the safety concerns expressed by SmithKline Beecham (SB), provided that data is acceptable. In addition, the fact that Compazine is generally used in acute situations also supports this approach.

- SB agreed to submit the simulation data within a few days and requested expedited consideration due to the imminent closing of the SB Spring Garden Street facility. The Division will try and accommodate this request as the workload permits.

/S/

Anna M. Homonnay-Weikel, R.Ph.
Project Manager

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-019

Smithkline Beecham Pharmaceuticals
Attention: Dale E. Stockbower
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

OCT 28 1998

Dear Ms. Stockbower:

Please refer to your new drug application dated September 29, 1997, received October 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Compazine[R] (prochlorperazine maleate) Spansule[R] Capsules.

We acknowledge receipt of your amendments dated April 30, May 18, and August 7, 1998. We also refer to our Not Approvable letter dated February 19, 1998.

The User Fee goal date for this application is November 4, 1998.

This application provides for a new formulation of the drug product involving a new drug

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

BIOPHARMACEUTICS ISSUES:

1. The two strengths of Compazine Spansule capsules have undergone a major formulation change, where, importantly, the drug release controlling mechanism has been modified. From a pharmacokinetic standpoint this would necessitate the characterization of the new Spansule formulation relative to the current one at multiple dosing where the end of dosing interval levels, viz., the Cmins, can be assessed. It is important to ascertain whether or not the levels of the drug produced at the end of the dosing interval from the new formulation are equal to

those seen for the current formulation, particularly in the absence a clinical study, as is the situation in this case. Thus, we ask that you conduct a multiple dose study comparing the highest strength of your planned to be marketed Spansule capsule to the currently marketed Spansule capsule.

2. You should also conduct a food study on the highest strength of your new Spansule capsule to characterize the effect of food.

3. Further, these data should be provided for all other capsule strengths that you propose to market.

In addition, there are chemistry deficiencies that, while not the basis for the nonapproval action, need to be addressed:

CHEMISTRY ISSUES:

1. We note your commitment to provide the identity when they become known. Please provide information regarding your technical plans to identify them as well as your anticipated time line to fulfill this commitment.

2. We note your proposed specification in the drug product. Please change the significant figures of this specification to

3. Please provide a proposed specification for the for the drug product which is based on and reflective of the data

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you should have any questions regarding the policy set forth in this Not Approvable letter, please contact Ms. Anna M. Homonnay-Weikel, R.Ph., Project Manager, at (301)594-5535 to arrange for a teleconference or a meeting for further discussion with the review team.

Sincerely yours,

/S/ 10/28/03

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL