DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

21-019

NDA ~~11-000~~ [redacted]

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

FEB 19 1998

Dear Ms. Stockbower:

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

The User Fee goal date for this application is April 1, 1998.

These supplemental applications provide for reformulation of the drug product [redacted] and for International Processing Center (IPC), Winchester, KY, as an alternate manufacturing site [redacted]

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

We have determined that the results of the submitted bioequivalence study show that the new SR formulation is not bioequivalent to the currently marketed Compazine Spansule since the C_{max} falls outside of the acceptance criteria [redacted]

We also have the following comments and requests for information that should be addressed:

CHEMISTRY ISSUES:

1. We note that the drug substance was not tested for the [redacted] at the initial time point and that there are no limits set. Testing for these [redacted] should be conducted at the initial time point in order to identify them and set limits. Additional testing should be conducted on earlier lots of the drug substance to verify that these same [redacted] were present.

2. Limits should be set for for [redacted] in the drug product.

SmithKline Beecham
Pharmaceuticals

August 24, 1999

ORIG AMENDMENT

N (BL)

NDA 21-019/Amendment
Compazine® (prochlorperazine maleate)
Spansule® Capsules
Pages 000001-000021

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

AUG 25 1999

RECEIVED HFD-120

Paul D. Leber, M.D., 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

Response to FDA Request for Information

Dear Dr. Leber:

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 commercial Compazine® Spansule® product, and site transfer from the SB Spring Garden Street facility, in Philadelphia, PA. Additional reference is made to our April 27, 1999 submission, which responded to the Agency's approvable letter of March 9, 1999, and to our correspondence of July 30, which requested that FDA review our submission in advance of the October 29, 1999 User Fee date to minimize that time the product is out of stock, due to a recall situation.

Submitted herewith in duplicate, in response to an August 20, 1999 request from Merril Mille, is a diskette containing the text of the draft labeling provided in the aforementioned April 27 submission. The electronic format of the document is Word 97, and it is annotated using a 'strikethrough' font or 'double underline' font to indicate deletions or additions, respectively. The chemical structure and a specific version identification number, with issue date, will be incorporated into final printed labeling accordingly.

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

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

For convenience of review, the draft labeling corresponding to the text on the diskette is also provided.

We thank you for your assistance in prioritizing this NDA review in advance of the assigned User Fee date. If you have any questions about this submission, please feel free to contact Lisa Reed at (610) 917-5704 (phone) or (610) 917-4704 (fax).

Sincerely,

Dale E. Stockbower
Assistant Director
N.A. Regulatory Affairs

Desk Copy: Merril Mille (HFD-120, letter only)

SB

SmithKline Beecham

Pharmaceuticals

July 30, 1999

NDA 21-019
Compazine® (prochlorperazine maleate)
Spansule® Capsules
Pages 000001-000005

NC DUPLICATE

NEW CORRESP

CENTER FOR DRUG EVALUATION AND RESEARCH

AUG 03 1999

RECEIVED HFD-120

Paul D. Leber, M.D., 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: Correspondence – Out of Stock Situation
Expedited Review Requested

Dear Dr. Leber:

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 commercial Compazine® Spansule® product, and site transfer from the SB Spring Garden Street facility, in Philadelphia, PA.

Additional reference is made to our April 27, 1999 submission, which contained draft labeling and a request for reconsideration of the drug release limit, in response to the Agency's approvable letter of March 9, 1999. This response has been assigned a User Fee due date of October 29, 1999.

Due to a recall of all Compazine® Spansule® capsules in the market place, and a hold on product in inventory, this product is currently out of stock. Consequently, we hereby request the Agency's assistance in expediting final approval of NDA 21-019 by the end of August, 1999, in order to minimize the disruption of supply to patients in need of this medication. Please note that the Compazine® Spansule® capsule formulation is the only available controlled release dosage form of prochlorperazine.

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

In a July 20, 1999 telephone conversation Merril Mille and I discussed this out of stock situation. The recall is being coordinated through the Philadelphia District Office and is due to a lack of assurance that the product will meet its specifications throughout the expiry period. Per Mr. Mille's recommendation we are providing this submission to inform the Division of the situation, and detail relevant timings for resupplying the product to the market place.

The Spring Garden Street manufacturing facility was closed June 30, 1999, so SB cannot supply the current Compazine® Spansule® capsule formulation. All future commercial supplies of Compazine® Spansule® capsules must be the reformulated product from the new manufacturing site, International Processing Corp. (IPC) Kentucky, identified in NDA 21-019. IPC will begin production of validation lots of both 10 mg and 15 mg Compazine® Spansule® capsules on August 9, 1999. Product will be available for packaging by the end of August, 1999. Printing of prescribing information is dependent upon the Agency's approval of labeling; draft labeling was contained in our April 27, 1999 submission. Packaged product should be available for distribution approximately three weeks after receipt of FDA approved labeling text.

We thank you in advance for your assistance in prioritizing this NDA approval in advance of the assigned User Fee date. If you have any questions about this information, or about our April 27, 1999 response, please feel free to contact me at (610) 917-6704 (phone) or (610) 917-4704 (fax).

Sincerely,

Dale E. Stockbower

Dale E. Stockbower
Assistant Director
N.A. Regulatory Affairs

Desk Copy: Merril Mille (HFD-120)

SmithKline Beecham
Pharmaceuticals

DESK COPY

April 27, 1999

NDA 21-019
Compazine® (prochlorperazine maleate)
Spansule® Capsules
Pages 000001-000084

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 Approvable Letter

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 commercial 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 the Agency's approvable letter of March 9, 1999 (Attachment 1) wherein NDA 21-019 was found to be approvable pending incorporation of labeling changes to add a food effect statement, and revision of the proposed storage statement to be the same as the storage statement used for the current formulation (Items 1 and 2 of your March 9, 1999 letter). In addition, the Agency recommended that we assign a different dissolution specification to that which was proposed by SB (Item 3).

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

Provided herein are our responses to the approvable letter issue. Attachment 2 contains revised draft labeling and Attachment 3 provides information in support of the SB proposal for dissolution limits.

If you have any questions about this information, please feel free to contact me at (610) 917-6704.

Sincerely,

Dale E Stockbower.

Dale E. Stockbower
Assistant Director
US Regulatory Affairs

Desk Copy: Anna Marie Hommonay-Weikel

Field Copy: Cincinnati District Office - D. Grelle
Philadelphia District Office - D. Pagano (letter only)

SmithKline Beecham

DESK COPY

December 14, 1998

NDA 21-019
Compazine® (prochlorperazine maleate)
Spansule® Capsules
Pages 000001-000019

Paul D. Leber, M.D., 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

General Correspondence: Information for Telephone Conference

Dear Dr. Leber:

Reference is made to our new drug application of September 29, 1997 for Compazine® (prochlorperazine maleate) Spansule® Capsules, NDA 21-019 (previously designated NDA 11-000[redacted] This NDA provides Chemistry, Manufacturing and Controls information to describe the reformulation of the drug product as a replacement for the current commercial Compazine® Spansule® product, and to change the drug product manufacturing site from the SB Spring Garden Street facility, Philadelphia, PA to International Processing Center (IPC), Winchester, KY.

Additional reference is made to the not approvable letter of October 28, 1998, and to telephone discussions held with Anna-Marie Hommonay-Weikel on November 23 and 30, and December 8, 9 and 10, 1998 regarding that letter. As a result, a telephone conference has been arranged between FDA and SB for December 21, 1998, from 3:00 – 4:00 pm. As agreed, submitted herein is the list of SB participants for that telecon, our proposed agenda, and the information included in Attachment 2 of our November 23, 1998 submission, included as the basis for discussion. In addition to the archival and review copies submitted to the Division, five Desk Copies are provided to Ms. Hommonay-Weikel.

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

An Index to this submission is presented on page 000006. If you have any questions, please feel free to contact me at (610) 917-6704.

Sincerely,

Dale E Stockbower.

Dale E. Stockbower
Assistant Director
U.S. Regulatory Affairs

Desk Copy: Anna Marie Hommonay-Weikel (5 copies)

SmithKline Beecham

ORIGINAL

November 24, 1998

ORIG AMENDMENT
N (AZ) BZ
[redacted]

NDA 21-019/Amendment
Compazine® (prochlorperazine maleate)
Spansule® Capsules
Pages 000001-000027

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 25 1998
RECEIVED HFD-120

Paul D. Leber, M.D., 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

Request for Telephone Conference/ Response to Not Approvable Letter

Dear Dr. Leber:

Reference is made to our new drug application of September 29, 1997 for Compazine® (prochlorperazine maleate) Spansule® Capsules, NDA 21-019 (previously designated NDA 11-000[redacted]). This NDA provides Chemistry, Manufacturing and Controls information to describe the reformulation of the drug product as a replacement for the current commercial Compazine® Spansule® product, and to change the drug product manufacturing site from the SB Spring Garden Street facility, Philadelphia, PA to International Processing Center (IPC), Winchester, KY.

Additional reference is made to the not approvable letter of October 28, 1998, and to a telephone discussion I had with Anna-Marie Hommonay-Weikel on November 23, 1998 regarding that letter. As agreed, we hereby are submitting a written request for a telephone conference with Biopharmaceutics to discuss the not approvable letter, and the SB responses contained herein. We would greatly appreciate if this discussion could be held the week of November 30, since this letter has a significant impact on the planned December 11, 1998 closing of our current manufacturing facility.

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

Attachment 1 contains a copy of the October 28, 1998 Agency letter, which cites three Biopharmaceutics issues that are the subject of the not approvable status, and requests further information on three Chemistry issues. Our letter of November 5, 1998 notified you of our intent to respond to this letter.

Submitted herein are our responses to each item in your October 28, 1998 letter. **Attachment 2** contains responses to the three Biopharmaceutics issues, and **Attachment 3** contains responses to the three Chemistry issues.

An Index to this submission is presented on page 000006.

We trust the responses contained herein will allow prompt approval of this application, and look forward to the opportunity to discuss them with the Agency. If you have any questions, please feel free to contact me at (610) 917-6704.

Sincerely,

Dale E Stockbower.

Dale E. Stockbower
Assistant Director
U.S. Regulatory Affairs

Desk Copy: Anna Marie Hommonay-Weikel (2)

Field Copy: Cincinnati District Office - D. Grelle
Philadelphia District Office - D. Pagano (letter only)

SmithKline Beecham
Pharmaceuticals

ORIGINAL

August 7, 1998

NDA 21-019
Compazine® (prochlorperazine maleate)
Spansule® Capsules
Volume 1: pages 000001-000023

CENTER FOR DRUG EVALUATION
AND RESEARCH

AUG 11 1998

RECEIVED HFD-120

AMENDMENT

N(BB)

Paul D. Leber, M.D., 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

Amendment: Response to Information Request

Dear Dr. Leber:

Reference is made to our pending Supplemental New Drug Applications for Compazine® (prochlorperazine maleate) Spansule® capsules, NDA 11-000, submitted September 29, 1997 [redacted] which contained information pertaining to a reformulated Spansule capsule product and a change in the drug product manufacturing site from the SB Spring Garden Street facility, Philadelphia, PA to International Processing Center (IPC), Winchester, KY. Reference is also made to our April 30, 1998 response to your February 19, 1998 non-approvable letter wherein we provided our responses to each item in your letter with additional supporting information. NDA 11-000 was subsequently reassigned as NDA 21-019 per the Agency's letter dated June 18, 1998.

Further reference is made to a July 31, 1998 telephone conversation between Dr. Ray Baweja (FDA) and Ms. Lisa Marie Reed (SB) and subsequently with Ms. Dale Stockbower (SB), wherein Dr. Baweja requested re-analysis of the AUC data provided in BE study 011 (Formula Codes BA-AA and AT-AB) in our April 30, 1998 submission, Volume 1, page 000159. He requested that the 90% confidence intervals for AUC be calculated from AUC (0-inf) instead of AUC (0-t'), and that the dissolution method used to obtain the data provided on page 000021 be specified.

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

Submitted herein is our response to Dr. Baweja's July 31, 1998 request for information. Per Dr. Baweja's request the dissolution information was faxed to him on July 31, 1998 and a copy is provided herein in Attachment 1. Re-analysis for the Compazine BE study performed on log transformed data is provided in Attachment 2.

An Index to this submission is presented on page 000006.

If you have any questions regarding this information, please feel free to contact me at (610) 917-6704.

Sincerely,

Dale E. Stockbower

Dale E. Stockbower
Assistant Director
U.S. Regulatory Affairs

Desk Copy: FDA (HFD-860) - R. Baweja

Field Copy: Cincinnati District Office - D. Grelle
Philadelphia District Office - D. Pagano (letter only)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-019

MAY 13 1999

Mille

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

Dear Ms. Stockbower:

We acknowledge receipt on April 29, 1999 of your April 27, 1999 resubmission to your new drug application (NDA) for Compazine® (prochlorperazine maleate) Spansule® Capsules, 10 mg and 15 mg.

This resubmission contains revised draft labeling and addresses our request for a different dissolution specification, in response to our March 9, 1999 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is October 29, 1999.

Should you have any questions concerning this NDA, contact Merril Mille, R.Ph., Senior Regulatory Management Officer, at (301) 594-5528.

Sincerely,

/S/ 5/13/99

Russell G. Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research