CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40231

CORRESPONDENCE

ANDA 40-231

MAY 20 1997

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
Post Office Box 128
Conestee, SC 29636

Dear Madam:

Reference is made to your abbreviated new drug application submitted December 20, 1996, pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Chlorpromazine HCl Oral Concentrate, 30 mg/mL.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

pai Pharmaceutical Associates, Inc.

5cc(g)(2)(a)(ok)
Anna Marie H. Wickel
1/14/97

December 19, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA Chlorpromazine Hydrochloride Concentrate 30mg/mL

Dear Sir:

Enclosed is the abbreviated new drug application for the drug product Chlorpromazine Hydrochloride Concentrate 30 mg/mL in 4 oz and 16 oz PET containers and a 16 oz glass container.

We have answered comprehensively, responsibly, and to the best of our ability all required items on Form FDA 356h and have to the best of our knowledge replied to the requirements of 21 CFR Section 314.50 and 314.94 where applicable.

The Table of Contents explains the organization of the application which consists of two volumes. Volume 1 consists of Sections I-XIV and Volume 2 consists of Sections XV-XXI. Each separate section of the ANDA is split off by labeled dividers that contain both the section number of that section and brief description of the section's subject matter (e.g., I. Basis). These dividers correspond to the sections listed in the Table of Contents.

Pharmaceutical Associates, Inc. is filing an archival copy (in blue folder) that contains all the information required in the ANDA and a technical review copy (in red folder) which contains all the information in the archival copy. In addition, we are also providing, in green folders, three additional copies of the methods validation portion of the ANDA.

I certify that a true copy of this application has been provided to the Atlanta District Office.

Thank you for your consideration in this matter.

Sincerely yours,

RECEIVED
DEC 20 1996
GENERIC DRUGS

PHARMACEUTICAL ASSOCIATES, INC.
Kaye B McDonald
Kaye B. McDonald
Scientific Affairs Manager

Beach Products, Inc./Contract Sales
5220 South Manhattan Avenue
Tampa, FL 33611
Phone: (813) 839-6565
Fax: (813) 837-2511

Leadership and Integrity
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Pharmaceutical Associates Subsidiary
201 Delaware Street
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 277-8045

pai Pharmaceutical Associates, Inc.

FACSIMILE AMENDMENT

November 18, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: 40-231 Chlorpromazine Hydrochloride Oral Concentrate, USP 30mg/mL

Enclosed please find a revised Certificate of Analysis for the drug product with the limit of Chlorpromazine sulfoxide changed to our proposed release limits of %. The original testing was based on the USP method using thin layer chromatography. Using this method, there was no Chlorpromazine sulfoxide detected. We later developed the method for the sulfoxide and other impurities. When the product was tested after 9 months the sulfoxide was at % and no other impurities were detected. I have not listed other impurities on this COA because the USP method used is for the sulfoxide. If you have additional questions please let me know.

Sincerely,

Kaye McDonald

Kaye McDonald
Director of Scientfic Affairs

Beach Products, Inc. Contract Sales
5220 South Manhattan Avenue
Tampa, FL 33611
Phone: (813) 839-6063
Fax: (813) 837-2511

Leadership and Integrity
Since 1958

Pharmaceutical Associates Subsidiary
201 Delaware Street
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 277-8045

pai Pharmaceutical Associates, Inc.

MINOR AMENDMENT

September 21, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: 40-231 Chlorpromazine Hydrochloride Oral Concentrate, USP, 30 mg/mL

The following is in answer to the minor deficiency amendment of September 9, 1998.

A. Deficiencies

1. DMF remains inadequate. The DMF holder has been notified. Please do not respond until the DMF holder has notified you that they have answered to their deficiencies.

   Response: The holder of DMF has assured us that the deficiencies have been addressed. A copy of the letter is included on page 1.

2. Please provide the analytical methods to be used for examing the individual impurities and total impurities, for example, method, conditions and its entire procedure including relevant calculation and chromatograms. Please also provide the certificate of analysis to support the proposed specifications for the impurities, i.e., COA of the drug substance from the drug manufacturer and Pharmaceutical Associates, Inc., and COA of the drug product and stability data.

   Response: The analytical method for examing the individual and total impurities is included on pages 2 – 4 of our test method A copy is included on pages 2 – 10. Representative chromatograms are on pages 11 – 12. The COA for the drug substance from the manufacturer is included on page 14. They have a limit for a single impurity of NMT %. USP has a limit of NMT % for other alkylated phenothiazines in the drug substance. Our proposed limits for the drug product for Chlorpromazine Sulfoxide are not more than % initially, and not more than % for stability. These are based on the USP limit for the Sulfoxide of NMT %. Our limit for individual impurities for release of NMT % and total of % is based on the raw material limits for individual impurities. A COA for the drug product is included on page 16. The USP method for sulfoxide was run at

Beach Products, Inc. Contract Sales
5220 South Manhattan Avenue
Tampa, FL 33611
Phone: (813) 839-6565
Fax: (813) 837-2511

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Pharmaceutical Associates Subsidiary
201 Delaware Street
Greenville, SC 29605
Phone: (864) 277-7282
Fax: (864) 277-8045

that time. The alternate method was developed and used for stability testing. Shelf stability data is included on pages 17 – 18.

3. On page 124 of the original application, under heavy metals and chromatographic purity, the results reported as "conform" are not acceptable. The quantitative test data should be given in the certificate of analysis. The analytical method, for example, or USP 23, should be provided for each test in the report form.

   Response: The certificate of analysis for the drug substance has been revised and is on pages 19 – 20.

   Also included on pages 21 – 25 are tabular presentations of our raw material specifications, bulk product, packaged (finished) product, and stability specifications. The impurity method for the raw material was developed as a result of a deficiency letter for our Chlorpromazine Hydrochloride Oral Concentrate, USP, 100 mg/mL, ANDA 40-224. This test was not in effect when this lot of raw material was tested.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. In the March 5, 1998 amendment, page 007 PFC 9772 Ideal Vanilla 1% v/v, 0.01 mL per mL, quantity gallons, the formula required volume should be mL not L.

   Response: This was a typographical error. A corrected copy is included on page 26.

2. In the March 5, 1998 amendment, pages 021 and 028, under the formulation, glycerin, USP % each mL should contain mL not mg.

   Response: These were typographical errors. Corrections are included on pages 27 – 30.

LABELING DEFICIENCIES

INSERT – On pages 36 – 41 are 2 × 12 copies of final print for our insert, incorporating all of your comments.

A side by side comparison of our proposed insert and our last submission is included on pages 31 – 35.

We have answered all of your questions to the best of our knowledge. If you have further questions, please let us know.

Sincerely yours,
PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

pai Pharmaceutical Associates, Inc.

March 5,1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: 40-231 Chlorpromazine Hydrochloride Oral Concentrate USP, 30 mg/mL.

Enclosed find form 356h for a major deficiency amendment

A. Deficiencies:

1. DMF was found to be inadequate. The DMF holder has been notified.

   Response: the holder of DMF has assured us that the deficiencies have been addressed.

2. The expression in percentage for the formula composition of the Chlorpromazine Hydrochloride Oral Concentrate USP, glycerin USP is expressed in %v/v and saccharin sodium, sodium benzoate, edeteate calcium disodium, citric acid, ascorbic acid and sodium bisulfate are expressed in %w/v in the same formula. Please provide the consistent percent expressions for the formula of the subject product.

   Response: The formula composition statements have been revised to include % v/v for all liquids and % w/v for all solids. We measure liquids such as glycerin and propylene glycol by volume and weigh all solids. Revised composition statements are included on pages 5-11 of this amendment.

3. In the manufacturer's certificate of analysis for chlorpromazine hydrochloride drug substance, two numbers are given % and %, under the item color. Please explain.

   Response: The manufacturer has informed us that the two numbers under item color are information that is requested by another customer and is of no significance to us. The numbers do represent transmittance at two different wavelengths.

4. On page 507, under the system suitability test, resolution is not less than between the sodium benzoate peak and the previous peak. It is not clear which one is the previous peak. Please specify the retention time to identify the peak to be used for calculating the resolution factor.

Response: The method has been revised to clarify the peak to be used to calculate the resolution factor. The revised method is included on pages 12 - 20 of this amendment.

5. In addition to the and peak tailing factor, three parameters, i.e., capacity factor, number of theoretical plates (column efficiency), and resolution factor should also be calculated and reported in the system suitability tests.

Response: Capacity factors, number of theoretical plates and resolution factor have been added to the system suitability tests. The revised method is included on pages 12 - 20 of this amendment.

6. Please provide available room temperature (25° - 30°C) stability data for the Chlorpromazine HCl Oral Concentrate USP, 30mg/mL (lot #13836) stored in the 4oz. and 16oz. PET containers.

Response: All available room temperature stability data for the 4 oz. is included on page 21 of this amendment. Due to marketing considerations, we wish to withdraw the 16oz container at this time. The following pages for the 16oz. size can be disregarded.

Pages 48-56
301-306
373-446
651-654

7. Please explain the reason why sodium benzoate should go to % for the stability samples.

Response: Sodium Benzoate is not expected to go to % for stability. The limits have been revised with the revised stability specifications included on pages 22 - 23 of this amendment.

8. Please provide the limits for other individual and total impurities of the finished product at the time of product release and for stability.

Response: The limits for other and total impurities are provided in the release and stability specifications on pages 24 - 25 of this amendment.

9. Please provide a quantitative color specification for the finished product and stability samples.

Response: A quantitative color specification has been developed and is included as part of the method on pages 12 - 20. The shelf stability samples were tested at 18 months. The results are on page 26.

10. On page 639, under II. Assay for Chlorpromazine HCl, the concentration of the Chlorpromazine HCl Oral Concentrate USP should be 30 mg/mL. On pages 648, 649, 651 and 653 under the % of label claim, the concentration of Chlorpromazine HCl Oral Concentrate USP should be 30mg/mL. Please provide the correct concentration of Chlorpromazine HC1 Oral Concentrate USP in you stability reports.

Response: The concentration for Chlorpromazine HCl in the assay has been corrected. The revised sheets are on pages 22 – 23 and 27 - 28 of this amendment. Pages 651 and 653 are to be disregarded, since we are not seeking approval for the 16 oz at this time.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your ANDA application relative to the drug substance and drug product manufactures, packaging and stability testing must be in compliance with cGMP's at the time of approval.

Response: We acknowledge that the firms referenced in the ANDA application relative to the drug substances and drug product manufacture packaging and stability testing must be in compliance with CGMP; s at the time of approval.

2. Your analytical methodology is not identical to the US Pharmaceutical methods for the final drug product. Please be advised that the USP methods are the regulatory methods and will prevail in the event of any dispute.

Response: We acknowledge that our analytical methodology is not identical to the US Pharmacopial methods for the final drug product and that the USP methods for the final drug product. Please be advised that the USP methods are the regulatory methods and will prevail in the event of any dispute.

LABELING DEFICIENCIES

1. **Container:** We wish to withdraw the 16-oz. container at this time due to marketing considerations. The following pages for the 16oz. size can be disregarded.

Pages 48-56
301-306
373 – 446
651 – 654

Our 30mg/mL will use green for labeling and carton, and the 100 mg/mL will be red.

On pages 52 - 55 are 2x12 copies of final print for our container labels incorporating all of your comments.

2. **Carton:** On pages 56 - 67 are 2x12 copies of final print for our cartons incorporating all of your comments.

3. **Inserts:** On page 68 - 73 are 2 x 12 copies of final print for our insert.

A side by side comparison of our proposed labeling and our last submission is included on pages 29 - 51.

We have answered all of your questions to the best of our knowledge. If you have further questions, please let us know.

Sincerely Yours,
PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs