CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40226

CORRESPONDENCE

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

August 7, 1997

ORIG AMENDMENT

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

RE: Perphenazine Tablets, USP
2 mg, 4 mg, 8 mg, 16 mg
ANDA 40-226

MINOR AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted December 6, 1996 and your letter dated July 7, 1997. Each of the points in your facsimile is stated, followed by our response.

A. **Deficiencies:**

1. **Please revise your in-process controls to include specifications for blending assay for the ganulate. Also the specifications for the release of the finished drug product and the stability should be revised regarding the limits for the related substances and impurities based on your data to not more than % for perphenazine sulfoxide, not more than % for individual unknown impurity and not more than % for total related substances.**

Attachment I - Revised in-process specifications to include blend assay results

Attachment II -Revised finished product specifications for each lot of product

The limit for perphenazine sulfoxide was revised to NMT %. The raw material specification for perphenazine sulfoxide is NMT %, however since perphenazine sulfoxide is a degradant and not an impurity it is a possibility that the perphenazine sulfoxide could be greater

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GENERIC DRUGS

than % in the finished product. Therefore, Vintage has revised their specification to a limit of NMT %. The specifications for the individual unknown and the total related substances have been revised to % and %, respectively, as requested.

2. **Please specify the type of the machine to be used in the coating. Also include flow rate (coating) range, atomization air volume range, nozzle distance to tablet range, and number of spray guns.**

3. **Please provide all available room temperature stability data.**

Attachment V - Room temperature stability data with new limits as stated in deficiency #4

4. **Please revise your specifications for stability regarding the perphenazine sulfoxide to not more than % and total not more than % based on your data.**

Attachment V - Room temperature data reports with revised specifications

Attachment VI -Accelerated stability data reports with revised specifications

The limit for perphenazine sulfoxide has been set for % due to the fact that the real time data at 24 months shows data to be greater than %. The limit of % was set to reflect this data and to allow for possible extension of expiration date in the future based on real time data. The specification for other individual impurities has been set at NMT % for each impurity and a total of NMT % for all related substances and impurities.

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 application regarding the manufacturing and testing of the drug product should be in compliance with CGMP's at the time of the approval.

Labeling Deficiencies:

1. CONTAINER (100s, 500s, 1000s)

Revise to delete except on container labels for the 16mg strength.

Attachment VII - Revised container labels

2. INSERT

a. GENERAL COMMENTS

i. Throughout the text, only capitalize the established name when sentence structure warrants.

ii. Delete the use of in the text except in the DESCRIPTION and HOW SUPPLIED sections.

b. DESCRIPTION

i. Revise to read "molecular formula".

ii. Revise to include the molecular weight and structural formula as seen in USP 23.

iii. Revise so that the second sentence begins a new paragraph and reads as follows: Each tablet, for oral administration, contains perphenazine 2 mg, 4mg, 8mg, and 16mg. In addition, each tablet contains the following inactive ingredients: acetone....

iv. Lactose has two monographs. Revise to include the one used in your product (e.g., lactose monohydrate).

c. ACTIONS

Revise section heading to read, CLINICAL PHARMACOLOGY.

d. INDICATIONS

i. Revise sections heading to read, INDICATIONS AND USAGE

ii. Revise the first paragraph to read, Perphenazine Tablets, USP are indicated.....

iii. Revise the second paragraph to read, Perphenazine has not been shown effective in...

e. CONTRAINDICATIONS

Revise the first sentence to read, Perphenazine tablets are...

f. WARNINGS

i. Revise the first sentence of the second paragraph to read,...neuroleptic drugs administered....

ii. Revise the sixth paragraph to read, ...please refer to PRECAUTIONS, Information...

iii. Neuroleptic Malignant Syndrome (NMS)

A) Revise format of subsection heading to be consistent throughout your labeling.

B) Revise the first sentence of the fourth paragraph to read,...the potential reintroduction...

C) Revise the third, sentence of the fifth paragraph to read,...the use of phenothiazines and is...

iv. Usage in Pregnancy

Revise the first sentence to read, Safe use of perphenazine during...

g. PRECAUTIONS

i. Revise the ultimate sentence of the tenth paragraph to read,...treatment with the drug should...

ii. Information for Patients

Revise the first sentence of the second paragraph to read,...patients exposed chronically to...

h. ADVERSE REACTIONS

i. CNS Effects

A) Other CNS Effects - Revise to read,...fluid proteins...(spelling)

B) Revise to add the following as a new category heading for the fourth paragraph: Neuroleptic Malignant Syndrome (NMS)

ii. Autonomic Effects

Revise the second paragraph to read,...with phenothiazine therapy...

iii. Other effects

Revise subsection to read, "Other Effects".

i. OVERDOSAGE

i. Revise to make OVERDOSAGE the section that immediately follows ADVERSE REACTIONS. You are referred to 21 CFR 201.56 (d)(4) for further guidance.

ii. Revise the sixth paragraph to read,...since perphenazine...(spelling).

iii. Revise the seventh paragraph to read,...from perphenazine...(spelling).

j. HOW SUPPLIED

i. Revise the storage temperature recommendation to read, store at controlled room temperature 15 - 30 C(59 -86 F) to be consistent with the storage statement on container labels.

ii. You are encouraged to revise to include: Dispense in a tight, light-resistant container.

iii. You are encouraged to include the "Caution: Federal law..." statement.

iv. Revise to include a description of the scoring configuration of your tablets (i.e., sugar coated, unscored...)

Attachment VIII - Revised inserts

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Attachment VII - Container labels
Attachment VIII - Insert labeling

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all difference annotated and explained.

Attachment IX - Side-by-side comparison, labels
Attachment X - Side-by-side comparison, inserts

This completes our response to the facsimile amendment issued. If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 23, 1997

N/AB

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

RE: Perphenazine Tablets, USP
2 mg, 4 mg, 8 mg, 16 mg
ANDA 40-226

BIOEQUIVALENCE AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted December 6, 1996, our amendments dated August 7, 1997 and September 12, 1997 and your letters dated July 7, 1997 and November 30, 1997.

Attachment I contains the the long-term stability study data as requested in your letter of November 30, 1997.

If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 30, 1998

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

RE: Minor Amendment , ANDA 40-226
Perphenazine Tablets, USP
2 mg, 4 mg, 8 mg, 16 mg

Dear Sir

As per our phone conversation of 12/29/98, please find the revised in-process granulation specifications.

If I can be for further assistance or if you have any questions, please contact Rebecca Childers or John Dambrauskas at (704) 596-0516.

Sincerely,

Rebecca Childers
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 22, 1998

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

NDA ORIG AMENDMENT
N/AM1

RE: Perphenazine Tablets, USP
2 mg, 4 mg, 8 mg, 16 mg
ANDA 40-226
TELEPHONE AMENDMENT

Dear Sir;

Per our phone conversation, please find attached the following documents:

Batch Production Record, page 3 and 4

Page 3 of the Batch Production Record has the instructions for pulling the composite sample and the amount of sample to be pulled

Page 4 of the Batch Production Record includes the specifications for the blend analysis

In-Process Specifications

In-Process Blend Testing Procedure

We look forward to your early response. If you have any questions or coments regarding this application, please contact the undersigned, or as an alternate, Mr. John Dambrauskas, General Manager, at Tel (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC

Rebecca Childers
Manager, Regulatory Affairs

[illegible]

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 21, 1998

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

NDA ORIG AMENDMENT
N/An1

RE: Perphenazine Tablets, USP
2 mg, 4 mg, 8mg, 16 mg
ANDA 40-226
TELEPHONE AMENDMENT

Dear Sir:

Per our phone conversation, please find attached the following documents:

Batch Production Record, page 3 and 4.

Page 3 of the Batch Production Record has the instructions for pulling the composite sample and the amount of sample to be pulled.

Page 4 of the Batch Production Record includes the specifications for the blend analysis.

In-Process Specifications

In-process Blend Testing Procedure

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Mr. John Dambrauskas, General Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

Rebecca Childers
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 9, 1998

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

NDA ORIG AMENDMENT
N/AM1

RE: Minor Amendment , ANDA 40-226
Perphenazine Tablets, USP
2 mg, 4 mg, 8 mg, 16 mg

Dear Sir

Please refer to the Vintage original ANDA, submitted December 6, 1996, amendments dated August 7, 1997, December 23, 1997 and January 22, 1998, and FDA's letter dated March 6, 1998.

Enclosed you will find our response to the deficiency as outlined in the FDA letter of March 6, 1998.

If I can be for further assistance or if you have any questions, please contact Rebecca Childers or John Dambrauskas at (704) 596-0516.

Sincerely,

Rebecca Childers
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

ORIG AMENDMENT

N/RM

January 22, 1998

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

RE: Perphenazine Tablets, USP
2 mg, 4 mg, 8 mg, 16 mg
ANDA 40-226

TELEPHONE AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted December 6, 1996, our amendments dated August 7, 1997, September 12, 1997 and your telephone call of January 21, 1998 and your letters dated July 7, 1997 and November 30, 1997.

As requested in your telephone call the limits for perphenazine sulfoxide has changed to %. This change was submitted in our telephone amendment dated September 12 ,1997. This amendment is a copy of the September 12 amendment. Included is revised stability data reports for accelerated and room temperature stability.

If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 6, 1996

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

Dear Sir:

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an original Abbreviated New Drug Application for:

Perphenazine Tablets, USP
2 mg, 4 mg, 8 mg, 16 mg

In-vivo and in-vitro bioequivalence studies are included in section VI.

The archival copy of the ANDA consists of ten volumes. The review copy consists of five red-jacketed chemistry & manufacturing volumes and six separately bound, orange-jacketed bioequivalence volumes. All volumes contain a complete Table of Contents. The following items are included immediately following the NDA Form 356h:

-Prescription Status Statement
-Debarment/Conviction Certification
-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Mr. John Schultz, General Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

Rebecca A. Thurman
Manager, Regulatory Affairs