CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40254

CORRESPONDENCE

/.1

ANDA 40-254

OCT - 9 1997

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Trihexyphenidyl Hydrochloride Tablets USP 2 mg & 5 mg.

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

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-254

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

MAY 27 1997

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Trihexyphenidyl Hydrochloride Tablets USP
2 mg & 5 mg

DATE OF APPLICATION: April 28, 1997

DATE OF RECEIPT: April 30, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips 5/21/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

505(j)(2)(a)(ok)
Ana marie H. Weikel
5/22/97

April 28, 1997

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:

Trihexyphenidyl HCl Tablets, USP
2 mg & 5 mg

Vintage Pharmaceuticals, Inc. is registered as a manufacturer of controlled substances in schedules II, III, IV, and V, under DEA Registration No. RV0172976.

In-vitro bioequivalence studies are included in section VI.

The archival copy of the ANDA consists of two volumes. The review copy consists of two red-jacketed chemistry & manufacturing volumes, one separately bound and orange-jacketed bioequivalence volume. 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

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 10, 1998

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

RE: Telephone Amendment , ANDA 40-254
Trihexyphenidyl Hydrochloride Tablets, USP
2 mg and 5 mg
TELEPHONE AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted April 28, 1997 , your major amendment dated July 11, 1997, our response dated March 13, 1998, your telephone call of July 17, 1998 and your letter dated September 29, 1998, our response dated October 29, 1998, your telephone call of December 7, 1998 and your telephone call of December 10 , 1998..

Enclosed you will find revised in-process specifications for the granulation testing with the limits set at % and RSD of NMT %.

This completes our response to the facsimile amendment issued. 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

12-8-98
12-9-98
2.1

3241 rk Blvd.
Char 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 8, 1998

ORIG AMENDMENT
N/AM

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

RE: Telephone Amendment , ANDA 40-254
Trihexyphenidyl Hydrochloride Tablets, USP
2 mg and 5 mg
MINOR AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted April 28, 1997 , your major amendment dated July 11, 1997, our response dated March 13, 1998, your telephone call of July 17, 1998 and your letter dated September 29, 1998, our response dated October 29, 1998 and your telephone call of December 7, 1998.

Enclosed you will find revised in-process specifications for the granulation testing with the limits set at %.

This completes our response to the facsimile amendment issued. 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

October 29, 1998

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

RE: Telephone Amendment , ANDA 40-254
Trihexyphenidyl Hydrochloride Tablets, USP
2 mg and 5 mg

MINOR AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted April 28, 1997 , your major amendment dated July 11, 1997, our respponse dated March 13, 1998, your telephone call of July 17, 1998 and your letter dated September 29, 1998. Listed below are your requests followed by our response.

Request - Explain what Vintage will do in the future to prevent the effect of electrostatic on the product samples taken from the blend.

Response - Vintage will pull smaller blend samples allowing for the laboratory to test the entire sample instead of drawing an aliquot from the blend sample for testing. This will allow the laboratory to rinse the bottle to obtain all the product that had adhered to the sides of the glass bottle.

Request - Tighten blend granulation content uniformity specifications to % and RSD NMT %.

Response - Vintage does not feel that tighter content uniformity specifications will increase assurance that the tablets will fall within specifications. Due to the problems that can occur with blend sampling, Vintage does not feel that the specifications should be tighter than the USP specifications of % with RSD NMT %.

Request - It is not necessary to do assay on a composite blend sample and blend content uniformity

Response - The in-process specifications have been revised to include only blend uniformity specifications

This completes our response to the facsimile amendment issued. 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/A C

March 13, 1998

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

RE: Major Amendment , ANDA 40-254
Trihexyphenidyl Hydrochloride Tablets, USP
2 mg and 5 mg

MAJOR AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted April 28, 1997 and your major amendment dated July 11, 1997. Each of the points in your facsimile is stated, followed by our response.

1. **We request that you submit the results of vendor qualification testing for each of the excipients used in the formulation.**

   Attachment I - Results of vendor qualification

2. **A review of the process validation study indicates that problems ensuring blend uniformity were encountered. The data on p.216 show that the final blend had a potency range of % . The mean was 90.5% with an RSD of 1.6%. These results indicate low potency with some individual samples failing the specification limits of %. If such low results were obtained for the demonstration batch how will you achieve adequate potency for the production batch with is 10 times larger? Moreover, the validation was not that rigorous in that content uniformity was not performed on the granulation, only the tablets. We request that you explain the low results and conduct a more rigorous validation study on the blend. Reevaluation of the blending process and reformulation or other means to achieve better uniformity should be considered.**

RECEIVED
MAR 16 1998
GENERIC DRUGS

4. **We request revision of the release limit for tablet hardness to include an upper limit.**

   Attachment IV - Revised release specifications

5. **Based on the acquired data, we request that the release limit for total impurities be slightly reduced.**

   Attachment IV - Revised release specifications

6. **It appears that your modified analytical method still meets the system suitability requirement specified in the monograph for tailing factor and theoretical plates. However, you should revise the RSD limit to % in accordance with the USP monograph.**

   Attachment V - Revised analytical method

7. **We request that you expand the post-approval commitment regarding the withdrawal of out-of-spec products to state that "Deviations that do not affect the safety and efficacy for the product will be promptly discussed between the applicant and the reviewing division and must be reported to FDA under 21 CFR314.81 (b)(1)(ii)."**

   Attachment VI - Revised post-approval commitment

Labeling Deficiencies:

1. **GENERAL COMMENT:**

   i. **We encourage the use of "USP" in the established name on your labels and labeling.**

   ii. **When using the established name in all caps the "I" in "HCL" appears the same as does your capital "i" (see your container labels for reference). Please revise your labels and labeling to read "HCL" where the established name is in all capital letters.**

2. **CONTAINER 2 mg and 5 mg - 100s, 500s, 1000s**
   should read "Usual Dosage"

3. INSERT

i. GENERAL COMMENT

Replace "trihexyphenidyl HCl" with "trihexyphenidyl" throughout the insert except in the TITLE, DESCRIPTION, INDICATIONS AND USAGE and HOW SUPPLIED sections.

i. TITLE
Trihexyphenidyl Hydrochloride Tablets, USP

ii. DESCRIPTION

Revise this section to read:

Trihexyphenidyl HCl is a synthetic antispasmodic. Each tablet, for oral administration, contains 2 mg or 5 mg trihexyphenidyl HCl and the following inactive ingredients:...

Trihexyphenidyl HCl is a white, or slightly off white, crystalline powder, having not more than a very faint odor.

Trihexyphenidyl HCl is the substituted piperidine salt, ... Its molecular formula is $C_{20}H_{31}NO \cdot HCl$. The structural formula is ::

[insert structural formula as it appears in the USP 23 monograph]

iii. ACTIONS

a. Revise this section heading to read "CLINICAL PHARMACOLOGY"

b. Revise the first sentence to read:

Trihexyphenidyl exerts a direct...

iv. INDICATIONS

a. Revise this section heading to read "INDICATIONS AND USAGE"

b. Revise the first sentence to read:

Trihexyphenidyl HCl tablets are indicated...

v. **WARNING**

Revise the section heading to be "WARNINGS" (add "S").

vi. **HOW SUPPLIED**

a. **Trihexyphenidyl HCl tablets are available**

b. **Delete the word "a" from the "Caution: Federal law..." statement.**

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling.

Attachment VII - Revised labels
Attachment VIII - Revised inserts

Please note that we reserve 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 differences annotated and explained.

Attachment IX - Side by side comparison

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

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs