CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-361

CORRESPONDENCE

Anda 40-361
12/01

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

NDA ORIG AMENDMENT
N/AM

December 15, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

Reference is also made to your Minor Amendment Deficiency Letter for Chemistry, Manufacturing and Controls, dated November 22, 2000.

The following is stated in the November 22, 2000 letter:

DEFICIENCIES:

COMMENT 1

Please be aware that this application cannot be approved until the deficiencies regarding DMF been addressed satisfactorily by the DMF holder.

RESPONSE 1

Barr acknowledges the Agency's comment.

COMMENT 2

We acknowledge that you have lowered your impurity specification limits on release and stability for the drug product. We however believe that the limits you propose are still not justified by the data you have provided. You are requested to further lower these limits to be more in line with the actual data.

12/20/00

Page(s) 1

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12/15/00

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 40-361
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

- **Current Revised Blank Stability Test Specifications and Test Record.**
- **Current Revised Finished Product Test Method TM-437K.**
- **Current Interim Stability Report.**

Identical copies of this Minor Amendment have been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes the present Minor Amendment and response to the Agency's letter dated November 22, 2000. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur

Vice President, Quality and Regulatory Counsel

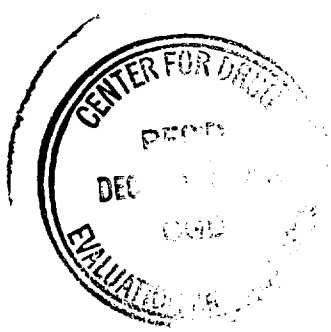
CM/jg

Enclosure

cc: New Jersey District Field Office

Baltimore District Field Office

This submission is comprised of **Pages 1 through 100**.



Document Certification

Barr Laboratories, Inc. hereby certifies that a field copy of this Minor Amendment for Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg is being submitted to the New Jersey and Baltimore district offices of the FDA. Barr Laboratories, Inc. further certifies that the field copy is a true copy of the material submitted to the Agency, in accordance with 21 CFR § 314.71(b)

Christine Mundkur

12-15-00

Christine Mundkur
Vice President, Quality and Regulatory Counsel
Barr Laboratories, Inc.

Date

noted jws
10/13/00

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

ANDA ORIG AMENDMENT

October 9, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

CENTER FOR DRUG EVALUATION AND RESEARCH
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OCT 10 2000
OGD

MINOR AMENDMENT

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

Reference is also made to your Minor Amendment Deficiency Letter for Chemistry, Manufacturing and Controls, dated August 31, 2000, and the September 11, 2000 phone conversation between Ms. Kassandra Sherrod, Project Manager, Team 7, Division of Chemistry II, OGD, FDA, and Joseph Greer of Barr Laboratories, Inc. regarding the reclassification of the August 31, 2000 Letter from a Major Amendment to Minor Amendment.

The following is stated in the August 31, 2000 letter:

DEFICIENCIES:

COMMENT 1

Regarding your request seeking approval for an alternate drug substance supplier in your April 5, 2000 amendment, we have the following comments:

a.

Page(s) 4

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10/9/00

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: ANDA 40-361
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

NMT
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Please see pages 78 through 148 for the following:

- **Current Revised Blank Finished Product Test Specifications and Test Record.**
- **Current Revised Blank Stability Test Specifications and Test Record.**
- **Current Revised Finished Product Test Method TM-437I.**
- **Current Interim Stability Report.**

Identical copies of this Minor Amendment has been provided to the New Jersey and Baltimore District Offices. A document certification is attached.

This completes the present Minor Amendment and response to the Agency's letter dated August 31, 2000. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

CM/jg
Enclosure
cc: New Jersey District Field Office
Baltimore District Field Office
This submission is comprised of **Pages 1 through 148**.

Barr Laboratories, Inc.

September 7, 2000

NEW CORRESP
NC

Gary Buehler, Deputy Director, HFD-601
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **CORRESPONDENCE**
ANDA 40-361
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

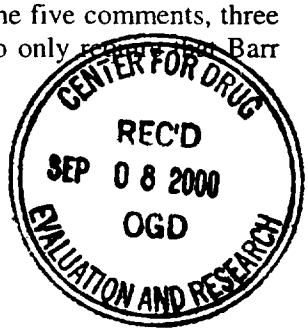
Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

Reference is also made to Barr's April 5, 2000 response to Major Amendment Letter dated July 29, 1999 and to Major Amendment Letter dated August 31, 2000 for Chemistry, Manufacturing and Controls in which the following is stated:

"The deficiencies presented below represent MAJOR deficiencies."

Barr respectfully requests that you reconsider the classification of the August 31, 2000 deficiency letter. This request is not typical of Barr Laboratories, Inc.; however, based upon the nature of the deficiencies noted, Barr believes that the classification of this deficiency letter as a "Major Amendment" is incorrect and unsubstantiated.

The deficiency letter is comprised of five deficiencies for the CMC portion. Of the five comments, three were addressed in our response letter dated April 5, 2000 and the remaining two only required that Barr take action by tightening impurities/degradation specifications.



The following is stated in the August 31, 2000 letter:

DEFICIENCIES:

COMMENT 1

Regarding your request seeking approval for an alternate drug substance supplier in your April 5, 2000 amendment, we have the following comments:

a.

1

F
reviewed.

9-12-00

Page(s) 2

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9/7/00

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

Based upon the minor nature of the CMC comments and the fact that the information for Comment Numbers 1, 3 and 4 were already provided in Barr's response to Major Amendment Letter dated April 5, 2000, Barr respectfully requests the Agency to reclassify the August 31, 2000 CMC comment letter as a Minor Amendment.

If you have any questions about the forgoing or Barr's responses, please do not hesitate to call me at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur

Vice President, Quality and Regulatory Counsel

cc: Kassandra Sherrod, Project Manager, Div. of Chemistry II, Team 7 by Fax (301) 443-3839.

This correspondence is comprised of **Pages 1 through 4.**

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 5, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

FPL
AC

MAJOR AMENDMENT

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

Reference is also made to your Major Amendment Letter for Chemistry, Manufacturing and Controls dated July 29, 1999 and the Labeling Comments dated September 29, 1999 in which the following is stated:

A. DEFICIENCIES:

COMMENT 1

You should include the n your Components and Composition statement for Calcium Sulfate.

RESPONSE 1

method KM – 331, is a combination of 90% Calcium Sulfate An

APR 06 2000
OGD
EVALUATION AND RESEARCH

Page(s) 10

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4/5/00

Barr Laboratories, Inc.

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OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

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ncluded

B. In addition to the deficiencies listed above, please note and acknowledge the follow

the

RESPONSE TO B

LABELING COMMENTS:

INSERT

a. DESCRIPTION

i. Revise the molecular weight to read, "Molecular Weight: 368.49"
ii. Include "compressible sugar" as one of the inactive ingredients.

b. INDICATIONS AND USAGE

Replace "children" with "pediatric patients (ages 3 to 16 years)

c. PRECAUTIONS

Pediatric Use

Replace "children" with "pediatric patients" in the second paragraph.

d. OVERDOSAGE

Treatment

Replace the first paragraph with the following:

"Consult with a Certified Poison Control Center for up-to-date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic, and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved."

e. DOSAGE AND ADMINISTRATION

Replace "children" with "pediatric patients" in the fourth, fifth and sixth paragraphs.

RESPONSE

Barr acknowledges the Agency's request for revising labeling for Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg. The revised, final printed labeling are provided in Attachment

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

XII. Side by side comparisons of the proposed labeling with that of the previously submitted labeling are also provided.

Please note that Barr is no longer interested in seeking approval for the package sizes of 500 tablets for the 5 mg strength, nor the package sizes of 500 and 1000 tablets for the 10 mg strength. Barr seeks to package both strengths in the package size of 100 tablets only.

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

Please note that with the exception of the new raw material vendor, no changes have been made to the manufacturing procedures for Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg. See Attachment B and D updated sections for manufacturing and packaging procedures. Barr has updated the manufacturing masters for both strengths to incorporate guidelines/specifications for tablet hardness, weight, thickness and friability.

In the original ANDA dated February 18, 1999, Barr originally submitted for the package size of 100 and 500 tablets for the 5 mg strength, and package size of 100, 500 and 1000 tablets for the 10 mg strength of Dextroamphetamine Sulfate Tablets, USP. The recently manufactured lots using s drug substance that are being submitted for approval were packaged in 30 and 100 tablets for both strengths. Please note that at the present time, Barr does not seek to market the 5 mg strength in the bottle size of 30 or 500 tablets, nor the 10 mg strength in the bottle size of 30, 500 and 1000 tablets. The proposed package size for commercial marketing for both strengths is 100 tablets.

An identical copy of this Major Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present Major Amendment and response to the Agency's letters dated July 29, 1999 and September 29, 1999. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 5, 2000

NEW CORRESP

NC/B10

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

BIOEQUIVALENCE AMENDMENT

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

Reference is made to Barr's Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg** submitted on February 18, 1999.

Reference is also made to your letter for Bioequivalence dated July 29, 1999 in which the following is stated:

COMMENT

Dissolution testing will need to be incorporated into the stability and quality control programs as specified in USP 23.

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RESPONSE

Barr acknowledges the Agency's statement regarding Dissolution testing. Dissolution is a routine analysis performed on both stability and finished products. Please note that

Barr Laboratories, Inc.

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OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 40-361**
DEXTROAMPHETAMINE SULFATE TABLETS, USP 5 MG AND 10 MG

Dissolution testing is in the test method for Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg. A copy of method TM-437C was included in the original submission.

Please note that method TM-437C has since been updated to TM-437H. This method still includes dissolution testing in accordance with the current USP. As an attachment to this response please find a copy of the finished product test method TM-437H.

This completes the present Bioequivalence Amendment and response to the Agency's letter dated July 29, 1999. If you have any questions, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

CM/ag
Enclosure
This submission is comprised of **Pages 1 through 00046**.

ANDA 40-361

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970-0519

MAR 16 1999

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: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

DATE OF APPLICATION: February 18, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 19, 1999

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,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ack for filing
S. Middleton 3/1/99

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

February 18, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

We are submitting herewith, in duplicate, an Abbreviated New Drug Application under section 505(j) of the Federal Food and Cosmetic Act for **Dextroamphetamine Sulfate Tablets, USP 5 mg and 10 mg.**

Barr would like the agency to note that the submission batches for each of these strengths of Dextroamphetamine Sulfate Tablets, USP were manufactured with active raw material supplied by '). Since the time of purchase and use of this drug substance in the referenced batches, the was a victim of a facility disaster, i.e., an explosion. The manufacturing facility no longer exists. Please see Section VIII 2. of this application for a brief summary of the date and affected location. Although the manufacturing site is no longer functional, Barr acquired a DMF authorization letter from for the active raw material that was used by Barr to manufacture the submission batches. In addition, after the approval of this application, Barr intends to use its remaining inventory of the material to manufacture future finished product batches until such time that we are able to locate and qualify an alternate source of active.

This application is provided in duplicate, both as an archival copy and a review copy. The archival copy of the application is contained in blue binders and consists of 3 volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 3 volumes. The bioequivalence part of the review copy is contained in an orange binder. The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The information submitted in this application is also in accord with the October 14, 1994 communication from Dr. Janet Woodcock, Director CDER.

RECEIVED
FEB 19 1999
GENERIC DRUGS

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992 is a Debarment Certification Statement. In accordance with 21 CFR §314.94 (d) (5), a "Field Copy" of this application has been forwarded to the New Jersey District Office.

Your earliest acknowledgment to this application will be very much appreciated. If you have any questions, please contact me at (914) 353-8432.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and Regulatory Counsel

CM/krg