CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40309

CORRESPONDENCE

ANDA 40-309

MAY 21 1998

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

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.

Reference is made to the telephone conversation dated April 28, 1998 and your correspondence dated May 11, 1998.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/500 mg

DATE OF APPLICATION: April 15, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 16, 1998

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:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

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

Barr Laboratories, Inc.

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

April 15, 1998

labeling review drafted 3/21/98 A. Vega

505(b)(2) A OK 5/14/98 Gregory S. Davis

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

We are submitting herewith, in duplicate, an Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/500 mg.

The application is provided both as an archival copy and a review copy. The archival copy of the application is contained in blue binders and consists of 2 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 2 volumes. The bioequivalence part of the review copy is contained in orange binder and consists of 1 volume.

The format of this application is in accordance with Office of Generic Drugs, Policy and Procedure Guide #30-91. The contents of this application have been compiled in accordance the October 14, 1994 communication from Dr. Janet Woodcock, Director (CDER) and Mr. Ronald Chesemore (ORA). Numerous SOPs are no longer submitted in the application; however, these procedures are kept current and are available for inspection by the FDA District Field Investigators.

Included in this application, and in accordance with the Generic Drug Enforcement Act of 1992, a Debarment Certification Statement with a List of Convictions Statement is provided in this application. In addition, in accordance with the FDA's Final Rule (Federal Register, Vol. 58, No. 172, September 8, 1993), a "Field Copy" of this application has been forwarded to the Baltimore, and New Jersey District Offices.

Please note that Barr is also submitting two other applications for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 2.5 mg/500 mg, 7.5mg/500 mg, 7.5 mg/650 mg, and 10 mg/650 mg, and 10 mg/650 mg, and 5 mg/500 mg and 7.5 mg/750 mg strengths, respectively, at the same time.

Your earliest acknowledgment to this application will be very much appreciated.

Sincerely

BARR LABORATORIES, INC.

Christine Mundkur,
Regulatory Counsel and Director of
Regulatory Affairs

CM:cad
Enclosures

Barr Laboratories, Inc.

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

July 11, 2000

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

REFERENCE: **TELEPHONE AMENDMENT**
ANDA 40-309
HYDROCODONE BITARTRATE AND ACETAMINOPHEN
TABLETS, USP
10 MG/500 MG

Reference is made to our Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 MG/500 MG, submitted on April 13, 1998.

Reference is also made to a discussion between Christine Mundkur of Barr Laboratories Inc. and Andrew Langowski of the Office of Generic Drugs on July 6, 2000. As requested by Mr. Langowski, we are providing updated Raw Materials Specification and Test Records for, Acetaminophen, USP and Hydrocodone Bitartrate, USP, to conform to USP 24.

Barr has also tightened the stability specification of [redacted]% for Hydrocodone Bitartrate and Acetaminophen Tablets, USP. Copies of the revised Acceptance Tests for In-Process and Finished Products and Marketed Product Stability Specifications and Test Records are provided.

Identical copies of this amendment have also been submitted to the New Jersey and Baltimore District Offices. If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely

BARR LABORATORIES, INC.

Christine Mundkur

Christine Mundkur,
Regulatory Counsel and Vice President of
Regulatory Affairs

Barr Laboratories, Inc.

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

July 11, 2000

Ms. Regina Brown
Pre-Approval Coordinator
Food and Drug Administration
120 North Center Drive
North Brunswick, New Jersey 08902

REFERENCE: **TELEPHONE AMENDMENT**
ANDA 40-309
HYDROCODONE BITARTRATE AND ACETAMINOPHEN
TABLETS, USP
10 MG/500 MG
FIELD COPY

In accordance with 21 CFR 314.96 (b), enclosed is a "Field Copy" of a "Telephone Amendment" for the above referenced product.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely

BARR LABORATORIES, INC.

Christine Mundkur,
Regulatory Counsel and Vice President of
Regulatory Affairs

Barr Laboratories, Inc.

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

April 12, 2000

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

NDA DRUG AMENDMENT AM

REFERENCE: **FACSIMILE AMENDMENT**
ANDA 40-309
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 10 MG/500 MG

Reference is made to our Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10mg/500 mg submitted on April 15, 1998.

Reference is also made to a facsimile deficiency received on January 18, 2000. Following are the deficiencies identified by the Agency in bold print followed by Barr's response.

Chemistry Deficiencies:

Note: Mailed Apr 4/17/00

CENTER FOR DRUG REC'D APR 13 2000 OGD EVALUATION AND RESEARCH

4/14/00

Redacted 2

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confidential

commercial

information

Chen

3. **We note that the limit has been revised to NMT %. Please the limit further, we recommend release and stability limits of NMT % and NMT %, respectively.**

RESPONSE

Barr revised the finished product release and stability specifications for in accordance with the agency's recommendation. The release specification is NMT % and the stability specification is NMT %. As a result of the specifications, it was necessary for Barr to The additional method validation report is provided in Attachment 4. The updated test method, finished product release test record and specification sheets and stability test record and specification sheets are provided in Attachment 5.

If you have any questions concerning this correspondence, 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 12, 2000

William L. Bargo
District Director
Baltimore District
Food and Drug Administration
900 Madison Avenue
Baltimore, Maryland 21201

REFERENCE: **FACSIMILE AMENDMENT**
ANDA 40-309
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP 10 MG/500 MG

Field Copy

In accordance with 21 CFR 314.96 (b), Barr Laboratories Inc. is submitting a Field Copy of a Facsimile Amendment for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/500 mg.

Barr certifies that the field copies are true copies of the technical sections of the Amendment. A Document Certification is provided with this correspondence.

If you have any questions concerning this amendment, 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

July 13, 1999

Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
AC

REFERENCE: **MAJOR AMENDMENT**
ANDA 40-309
HYDROCODONE BITARTRATE AND
ACETAMINOPHEN TABLETS, USP
10 MG/500 MG

Reference is made to our Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg/500 mg submitted on April 15, 1998.

Reference is also made to a deficiency letter received on November 30, 1998. Following are the deficiencies identified by the Agency in bold print followed by Barr's response.

Chemistry Deficiencies:

Redacted 9

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information

Chem. Deficiencies

ANDA 40-309
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
10 MG/500 MG

Bioequivalency Comments:

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

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 provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

RESPONSE

Please note that the dissolution testing as specified in USP 23 have been incorporated in our stability and quality control program.

APPEARS THIS WAY
ON ORIGINAL

ANDA 40-309
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
10 MG/500 MG

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. **Please note that since ANDAs 40-307, 40-308 and 40-309 share a common insert that these applications must be approved at the same time or the insert must be revised accordingly.**

   b. **Section 126 of Title I of the FDA Modernization Act of 1997, amend Section 503 (b) (4) of the Federal Food, Drug and Cosmetic Act to require, at a minimum, that prior to dispensing, the label of prescription products contain the symbol "Rx only". A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site: http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, " Frequently Asked Questions " offer guidance on placement of the symbol on all labels and labeling.**

   c. **The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement and accompanying asterisk from your labels and labeling**

   RESPONSE

   We acknowledge Agency's comment regarding the common insert, "Rx only" symbol and WARNING statement. Please refer to our response to Comments 2 and 3.

2. CONTAINER **100s and 500s (all strengths)**

   a. **Satisfactory, however see GENERAL COMMENTS (b) and (c) above.**

   b. **The changes as mentioned in (b) and (c) above may be done post-approval for the container labels.**

ANDA 40-309
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
10 MG/500 MG

Labeling Deficiencies (Continued):

RESPONSE

Barr will revise its container labels to replace the caution statement with the "Rx only" symbol during printing of the next production quantities.

3. **INSERT**

a. **DESCRIPTION**

i. **Revise the structural formula of hydrocodone bitartrate as follows:**

ii. **Third paragraph, last sentence – "It has ..." Rather than**

iii. **Revise the molecular weight of acetaminophen to read 151.17 as seen in USP 23.**

iv. **See GENERAL COMMENT (c) above.**

RESPONSE

The insert has been revised according to the above comments. The revised final printed insert is provided in Attachment K.

b. **HOW SUPPLIED**

i. **You have described the 10 mg/500 mg tablet as " light beige mottled" yet on page 15.00006 of ANDA 40-309 it states " Please comment and /or revise.**

RESPONSE

The description of 10 mg/500 mg tablet "light beige mottled" as it appears in the HOW SUPPLIED section is the correct description. Page 15-00006 of ANDA 40-309 is the executed finished product specification and test record that had the improper description. The finished product specification for 10 mg/500 mg tablet has been revised with proper tablet description and is provided in Attachment A.

ANDA 40-309
HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS, USP
10 MG/500 MG

Labeling Deficiencies (Continued):

ii. **See GENERAL COMMENT (b) above.**

RESPONSE

The insert has been revised according to the GENERAL COMMENT (b) above.

Please revise your insert labeling, as instructed above, and submit in final print.

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.

RESPONSE

The insert has been revised according to the above comments. The revised final printed insert is provided in Attachment K. A side-by-side comparison of revised insert with our last submission is provided in Attachment L with all differences annotated and explained.

Please note that Barr was just informed that during August 1997 to February 1998 [one of Barr's outside contract laboratory, has relocated their] Appropriate CGMP statement and Debarment certification is provided in Attachment M.

If you have any questions concerning this correspondence, 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