CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74918

CORRESPONDENCE

Barr Laboratories, Inc.

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

February 26, 1998

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

ORIG AMENDMENT
N/FA

TELEPHONE AMENDMENT

REFERENCE: **ANDA 74-918**
NALTREXONE HYDROCHLORIDE TABLETS, 50 MG

Reference is made to our pending Abbreviated New Drug Application submitted on June 27, 1996 under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Naltrexone Hydrochloride Tablets, 50 mg.**

Reference is also made to the telephone conversations between Ubrani Venkataram, Ph.D., Team Leader Chemistry, Branch VI, Florence Fang, Deputy Director, Division of Chemistry II, OGD, CDER, FDA and Christine Mundkur, Regulatory Counsel and Director of Regulatory Affairs, Barr Laboratories, Inc. on February 23 and 24, 1998.

In response to the telephone conversations, Barr commits to test for for production/commercial batches of Naltrexone Hydrochloride Tablets, 50 mg. In addition, as agreed upon by Barr and FDA, Barr revised the in-process tests at the Barr acknowledges that the in-process testing may not be deleted without prior approval from the Agency. Copies of the revised Quality Control Specification Test Record and Acceptance Tests for In-Process and Finished Products (TM-420E) for Naltrexone Hydrochloride Tablets, 50 are provided on **Pages 1 through 32**.

RECEIVED
1998
GENERIC DRUGS

... Continued

REFERENCE: **ANDA 74-918**
NALTREXONE HYDROCHLORIDE TABLETS, 50 MG

Please note that in preparation for launch, Barr Laboratories, Inc. has manufactured two process validation batches of Naltrexone Hydrochloride Tablets, 50 mg intended for commercial sale upon approval of the ANDA. As part of the process validation, Barr has extensively tested the Since these batches have already been manufactured and f process validation, the Agency agreed in the February 24, 1998 telephone conversation that Barr may sell these two batches as long th met the established specifications. For all future production/commercial batches, Barr will defined in the Quality Control Specification Test Record and Acceptance Tests for In-Process and Finished Products.

In addition, please be advised that an identical copy of this Telephone Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the Telephone Amendment to the agency's comments of February 23 and 24, 1998. 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
Regulatory Counsel and Director of
Regulatory Affairs

Enc.

cc: New Jersey District Office

This Submission is comprised of **Pages 1 through 32.**

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE

24-FEB-1998

I called the firm at the request of Florence Fang, Deputy Director, Chemistry II on 2/20/98 to request a clarification of their in-process tests and specifications (Amendment dated 10/13/97). Barr has indicated in their specs sheet that the test will be done where indicated. However, this test is not indicated anywhere in the additionally the drug product contains less than Ms. Mundkur said that she will consult with her colleagues and get back to me.

She called back on 2/23/98 and said the following: that the test is done if it is included in the spec sheet; in this instance the tests will be done for and no more. I suggested that this may not be acceptable since the product has we may need testing of batches until sufficient data is gathered. She then wanted to know if they could delete some of the since they are doing I asked her to propose their intentions.

She called back on 2/24/98. This time Florence Fang also participated in the meeting. Ms. Mundkur said that they would like to delete since the only difference between product testing is the This was not acceptable to us and Florence pointed out that the in-process tests are done to control each critical step of manufacturing. Ms. Mundkur then suggested that they would at least like to eliminate This was acceptable since these tests do not provide any added assurance to the product quality. We then asked Ms. Mundkur to explain what they will be doing. She said

She will submit a revised spec sheet indicating or production batches for validation and for release. She will specify their commitments in the cover letter. She will submit all this as a fax amendment in a few days. We said we look forward to reviewing it.

ANDA NUMBER

74-918

TELECON/MEETING

INITIATED BY
[] APPLICANT/SPONSOR
[x] FDA

MADE
[x] BY TELEPHONE
[] IN PERSON

PRODUCT NAME

Naltrexone HCl Tabs

FIRM NAME
Barr Labs

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Christine Mundkur
Regulatory Affairs

914-362-1100

SIGNATURE U.V. Venkataram 2/24/98

DIVISION II

Barr Laboratories, Inc.

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

January 20, 1998

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

FACSIMILE AMENDMENT

REFERENCE: **ANDA 74-918**
NALTREXONE HYDROCHLORIDE TABLETS, 50 MG

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Naltrexone Hydrochloride Tablets, 50 mg.**

Reference is also made to your letter dated December 31, 1997 in which the following is stated:

CHEMISTRY DEFICIENCY COMMENT:

REGARDING STABILITY:

PLEASE REVISE YOUR POST APPROVAL COMMITMENT AS FOLLOWS: ANY LOTS FOUND TO FALL OUTSIDE OF THE APPROVED SPECIFICATIONS WITHIN ITS EXPIRATION DATE WILL BE WITHDRAWN FROM THE MARKET.

RESPONSE:

Barr Laboratories, Inc. has revised commitment 3 of the post-approval stability commitments in accordance with 21 CFR §314.81 (b)(1)(ii). Specifically, as provided in 21 CFR, Barr commits to notify the appropriate FDA district of "any bacteriological contamination, or any significant chemical, physical or other change or deterioration in the drug product". After the notification and additional consultation with the FDA District, any lots found to fall outside of the approved specifications within it expiration date may be withdrawn from the market. On Page 13, enclosed please find revised post approval commitment.

Continued

REFERENCE: **ANDA 74-918**
NALTREXONE HYDROCHLORIDE TABLETS, 50 MG

LABELING DEFICIENCIES

COMMENT #1

GENERAL COMMENT:

THE MARKETING EXCLUSIVITY FOR USE OF THIS DRUG PRODUCT FOR ALCOHOL TREATMENT EXPIRES DECEMBER 30, 1997. PLEASE INCLUDE THIS INFORMATION IN THE PACKAGE INSERT LABELING AND UPDATE YOUR STATEMENT OF PATENT CERTIFICATION AND MARKETING EXCLUSIVITY ACCORDINGLY.

RESPONSE:

Enclosed on Page 1 please find 12 final printed package brochures which have been revised according to the Agency's recommendation. Also enclosed on Pages 2 through 12 please find side by side comparison of Barr's proposed package brochure with Barr's last submitted package brochure.

COMMENT #2

INSERT:

A. CLINICAL PHARMACOLOGY

I. PHARMACODYNAMIC ACTIONS

A). ADD THE FOLLOWING TEXT AS THE PENULTIMATE PARAGRAPH:

... Continued

THE MECHANISM OF ACTION OF NALTREXONE IN ALCOHOLISM IS NOT UNDERSTOOD: HOWEVER, INVOLVEMENT OF THE ENDOGENOUS OPIOID SYSTEM IS SUGGESTED BY PRECLINICAL DATA. NALTREXONE, AN OPIOID RECEPTOR ANTAGONIST, COMPETITIVELY BINDS TO SUCH RECEPTORS AND MAY BLOCK THE EFFECTS OF ENDOGENOUS OPIOIDS. OPIOID ANTAGONISTS HAVE BEEN SHOWN TO REDUCE ALCOHOL CONSUMPTION BY ANIMALS, AND NALTREXONE HAS BEEN SHOWN TO REDUCE ALCOHOL CONSUMPTION IN CLINICAL STUDIES.

B). REVISE THE LAST PARAGRAPH AS FOLLOWS:

... REACTION EITHER AS A RESULT OF OPIOID USE OR ETHANOL INGESTION.

II. ADD THE FOLLOWING AS THE FIRST SUBSECTION OF THE CLINICAL TRIALS SUBSECTION:

ALCOHOLISM: THE EFFICACY OF NALTREXONE AS AN AID TO THE TREATMENT OF ALCOHOLISM WAS TESTED IN PLACEBO-CONTROLLED, OUTPATIENT, DOUBLE BLIND TRIALS. THESE STUDIES USED A DOSE OF NALTREXONE HYDROCHLORIDE 50 MG ONCE DAILY FOR 12 WEEKS AS AN ADJUNCT TO SOCIAL AND PSYCHOTHERAPEUTIC METHODS WHEN GIVEN UNDER CONDITIONS THAT ENHANCED PATIENT COMPLIANCE. PATIENTS WITH PSYCHOSIS, DEMENTIA, AND SECONDARY PSYCHIATRIC DIAGNOSES WERE EXCLUDED FROM THESE STUDIES.

... Continued

IN ONE OF THESE STUDIES, 104 ALCOHOL-DEPENDENT PATIENTS WERE RANDOMIZED TO RECEIVE EITHER NALTREXONE HYDROCHLORIDE 50 MG ONCE DAILY OR PLACEBO. IN THIS STUDY NALTREXONE PROVED SUPERIOR TO PLACEBO IN MEASURES OF DRINKING INCLUDING ABSTENTION RATES (51% VS. 23%), NUMBER OF DRINKING DAYS, AND RELAPSE (31% VS. 60%). IN A SECOND STUDY WITH 82 ALCOHOL-DEPENDENT PATIENTS, THE GROUP OF PATIENTS RECEIVING NALTREXONE WERE SHOWN TO HAVE LOWER RELAPSE RATES (21% VS. 41%), LESS ALCOHOL CRAVING, AND FEWER DRINKING DAYS COMPARED WITH PATIENTS WHO RECEIVED PLACEBO, BUT THESE RESULTS DEPENDED ON THE SPECIFIC ANALYSIS USED.

THE CLINICAL USE OF NALTREXONE AS ADJUNCTIVE PHARMACOTHERAPY FOR THE TREATMENT OF ALCOHOLISM WAS ALSO EVALUATED IN A MULTICENTER SAFETY STUDY. THE STUDY OF 865 INDIVIDUALS WITH ALCOHOLISM INCLUDED PATIENTS WITH COMORBID PSYCHIATRIC CONDITIONS, CONCOMITANT MEDICATIONS, POLYSUBSTANCE ABUSE AND HIV DISEASE. RESULTS OF THIS STUDY DEMONSTRATED THAT THE SIDE EFFECT PROFILE OF NALTREXONE APPEARS TO BE SIMILAR IN BOTH ALCOHOLIC AND OPIOID DEPENDENT POPULATIONS, AND THAT SERIOUS SIDE EFFECTS ARE UNCOMMON.

IN THE CLINICAL STUDIES, TREATMENT WITH NALTREXONE SUPPORTED ABSTINENCE, PREVENTED RELAPSE AND DECREASED ALCOHOL CONSUMPTION. IN THE UNCONTROLLED STUDY, THE PATTERNS OF ABSTINENCE AND RELAPSE WERE SIMILAR TO THOSE OBSERVED IN THE CONTROLLED STUDIES.

NALTREXONE WAS NOT UNIFORMLY HELPFUL TO ALL PATIENTS, AND THE EXPECTED EFFECT OF THE DRUG IS A MODEST IMPROVEMENT IN THE OUTCOME OF CONVENTIONAL TREATMENT.

... Continued

III. ADD THE FOLLOWING AS THE SUBSECTION IMMEDIATELY FOLLOWING THE *INDIVIDUALIZATION OF DOSAGE* SUBSECTION:

TREATMENT OF ALCOHOLISM: THE PLACEBO-CONTROLLED STUDIES THAT DEMONSTRATED THE EFFICACY OF NALTREXONE AS AN ADJUNCTIVE TREATMENT OF ALCOHOLISM USED A DOSE REGIMEN OF NALTREXONE HYDROCHLORIDE 50 MG ONCE DAILY FOR UP TO 12 WEEKS. OTHER DOSE REGIMENS OR DURATIONS OF THERAPY WERE NOT STUDIED IN THESE TRIALS.

PHYSICIANS ARE ADVISED THAT 5 TO 15% OF PATIENTS TAKING NALTREXONE FOR ALCOHOLISM WILL COMPLAIN OF NON-SPECIFIC SIDE EFFECTS, CHIEFLY GASTROINTESTINAL UPSET. PRESCRIBING PHYSICIANS HAVE TRIED USING AN INITIAL 25 MG DOSE, SPLITTING THE DAILY DOSE, AND ADJUSTING THE TIME OF DOSING WITH LIMITED SUCCESS. NO DOSE OR PATTERN OF DOSING HAS BEEN SHOWN TO BE MORE EFFECTIVE THAN ANY OTHER IN REDUCING THESE COMPLAINTS FOR ALL PATIENTS.

IV. *TREATMENT OF NARCOTIC DEPENDENCE:*. LAST PARAGRAPH, FIRST SENTENCE -

... ADDICT POPULATION AND IN INITIAL CLINICAL TRIALS IN ALCOHOLISM. CLINICS ...

B. INDICATIONS AND USAGE

NALTREXONE HYDROCHLORIDE TABLETS ARE INDICATED IN THE TREATMENT OF ALCOHOL DEPENDENCE AND FOR THE BLOCKADE ...

... Continued

C. WARNINGS

REVISE THE FIRST SENTENCE OF THE SECOND PARAGRAPH FOLLOWING THE WARNINGS BOX AS FOLLOWS:

... RECOMMENDED FOR THE TREATMENT OF ALCOHOLISM OR OPIATE BLOCKADE ...

D. ADVERSE REACTIONS

I. ADD THE FOLLOWING TEXT AS THE FIRST PARAGRAPH:

DURING TWO RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 12 WEEK TRIALS TO EVALUATE THE EFFICACY OF NALTREXONE AS AN ADJUNCTIVE TREATMENT OF ALCOHOL DEPENDENCE, MOST PATIENTS TOLERATED NALTREXONE WELL. IN THESE STUDIES, A TOTAL OF 93 PATIENTS RECEIVED NALTREXONE HYDROCHLORIDE AT A DOSE OF 50 MG ONCE DAILY. FIVE OF THESE PATIENTS DISCONTINUED NALTREXONE BECAUSE OF NAUSEA. NO SERIOUS ADVERSE EVENTS WERE REPORTED DURING THESE TWO TRIALS.

II. REPORTED ADVERSE EVENTS, SECOND SENTENCE.

STUDIES IN ALCOHOLIC POPULATIONS AND IN VOLUNTEERS ...

III. ADD THE FOLLOWING TEXT AS THE SUBSECTION IMMEDIATELY FOLLOWING "REPORTED ADVERSE EVENTS":

... Continued

ALCOHOLISM:

IN AN OPEN LABEL SAFETY STUDY WITH APPROXIMATELY 570 INDIVIDUALS WITH ALCOHOLISM RECEIVING NALTREXONE, THE FOLLOWING NEW-ONSET ADVERSE REACTIONS OCCURRED IN 2% OR MORE OF THE PATIENTS: NAUSEA (10%), HEADACHE (7%), DIZZINESS (4%), NERVOUSNESS (4%), FATIGUE (4%), INSOMNIA (3%), VOMITING (3%), ANXIETY (2%) AND SOMNOLENCE (2%).

DEPRESSION (5 TO 7%), SUICIDAL IDEATION (2%), AND ATTEMPTED SUICIDE (<1%) HAVE BEEN REPORTED IN INDIVIDUALS ON NALTREXONE, PLACEBO AND IN CONCURRENT CONTROL GROUPS UNDERGOING TREATMENT FOR ALCOHOLISM. ALTHOUGH NO CAUSAL RELATIONSHIP WITH NALTREXONE IS SUSPECTED, PHYSICIANS SHOULD BE AWARE THAT TREATMENT WITH NALTREXONE DOES NOT REDUCE THE RISK OF SUICIDE IN THESE PATIENTS (SEE PRECAUTIONS).

E. DOSAGE AND ADMINISTRATION

I. ADD THE FOLLOWING TEXT AS THE FIRST SUBSECTION AFTER THE FIRST SENTENCE:

TREATMENT OF ALCOHOLISM:

A DOSE OF 50 MG ONCE DAILY IS RECOMMENDED FOR MOST PATIENTS (SEE CLINICAL PHARMACOLOGY, CLINICAL TRIALS, INDIVIDUALIZATION OF DOSAGE).

... Continued

NALTREXONE SHOULD BE CONSIDERED AS ONLY ONE OF MANY FACTORS DETERMINING THE SUCCESS OF TREATMENT OF ALCOHOLISM. FACTORS ASSOCIATED WITH A GOOD OUTCOME IN THE CLINICAL TRIALS WITH NALTREXONE WERE THE TYPE, INTENSITY, AND DURATION OF TREATMENT; APPROPRIATE MANAGEMENT OF COMORBID CONDITIONS; USE OF COMMUNITY-BASED SUPPORT GROUPS; AND GOOD MEDICATION COMPLIANCE. TO ACHIEVE THE BEST POSSIBLE TREATMENT OUTCOME, APPROPRIATE COMPLIANCE-ENHANCING TECHNIQUES SHOULD BE IMPLEMENTED FOR ALL COMPONENTS OF THE TREATMENT PROGRAM, ESPECIALLY MEDICATION COMPLIANCE.

II. INTRAVENOUS CHALLENGE:

"NALOXONE HYDROCHLORIDE" RATHER THAN "NALOXONE" THROUGHOUT THIS PARAGRAPH:

... Continued

OFFICE OF GENERIC DRUGS
FOOD AND DRUG ADMINISTRATION

REFERENCE: **ANDA 74-918**
NALTREXONE HYDROCHLORIDE TABLETS, 50 MG

RESPONSE:

Enclosed on Page 1 please find 12 final printed package brochures which have been revised according to the Agency's recommendations. Also enclosed on Pages 2 through 12 please find side by side comparison of Barr's proposed package brochure with Barr's last submitted package brochure.

Please note that as per the conversation with Mr. Charles Hopas on January 6, 1998, the following statement that was included in the innovator's labeling was added to Barr's revised package brochure:

Re: Information for Patients subsection, second sentence, added the words "... alcoholism or ...".

Please refer to the side by side comparison for reference.

In addition, please be advised that an identical copy of this Facsimile Amendment has been provided to the New Jersey District Office. A document certification is attached.

This completes the present Facsimile Amendment and response to FDA letter dated December 31, 1997. 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
Regulatory Counsel and Director of
Regulatory Affairs

Enc.

cc: New Jersey District Office
This Submission is comprised of **Pages 1 through 13.**

DEC 31 '98

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-918 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Naltrexone Hydrochloride Tablet, 50 mg.

The deficiencies presented below represent FACSIMILE deficiencies.

Chemistry Deficiency

Regarding stability:

Please revise your post-approval commitment as follows: Any lots found to fall outside of the approved specifications within its expiration date will be withdrawn from the market.

Sincerely yours,

for Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

FACSIMILE AMENDMENT

DEC 31 1997

ANDA 74-918

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Barr Laboratories, Inc. PHONE: 914-362-1100

ATTN: Christine Mundkur FAX: 914-~~353-3339~~ 362-2043

FROM: Timothy Ames PROJECT MANAGER (301) 827–5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated June 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Naltrexone Hydrochloride Tablets, 50 mg.

Reference is also made to your amendment(s) dated October 13, 1997.

Attached are 6 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\macros\faxfax.frm

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-918** Date of Submission: **May 22, 1997**

Applicant's Name: **Barr Laboratories, Inc.**

Established Name: **Naltrexone Hydrochloride Tablets, 50 mg**

Labeling Deficiencies:

1. GENERAL COMMENT:

   The marketing exclusivity for use of this drug product for alcohol treatment expires December 30, 1997. Please include this information in the package insert labeling and update your statement of patent certification and marketing exclusivity accordingly.

2. INSERT

   a. CLINICAL PHARMACOLOGY

      i. Pharmacodynamic Actions

         A). Add the following text as the penultimate paragraph:

         The mechanism of action of naltrexone in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data. Naltrexone, an opioid receptor antagonist, competitively binds to such receptors and may block the effects of endogenous opioids. Opioid antagonists have been shown to reduce alcohol consumption by animals, and naltrexone has been shown to reduce alcohol consumption in clinical studies.

         B). Revise the last paragraph as follows:

         ... reaction either as a result of opioid use or ethanol ingestion.

ii. Add the following as the first subsection of the Clinical Trials subsection:

Alcoholism: The efficacy of naltrexone as an aid to the treatment of alcoholism was tested in placebo-controlled, outpatient, double blind trials. These studies used a dose of naltrexone hydrochloride 50 mg once daily for 12 weeks as an adjunct to social and psychotherapeutic methods when given under conditions that enhanced patient compliance. Patients with psychosis, dementia, and secondary psychiatric diagnoses were excluded from these studies.

In one of these studies, 104 alcohol-dependent patients were randomized to receive either naltrexone hydrochloride 50 mg once daily or placebo. In this study naltrexone proved superior to placebo in measures of drinking including abstention rates (51% vs. 23%), number of drinking days, and relapse (31% vs. 60%). In a second study with 82 alcohol-dependent patients, the group of patients receiving naltrexone were shown to have lower relapse rates (21% vs. 41%), less alcohol craving, and fewer drinking days compared with patients who received placebo, but these results depended on the specific analysis used.

The clinical use of naltrexone as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multicenter safety study. The study of 865 individuals with alcoholism included patients with comorbid psychiatric conditions, concomitant medications, polysubstance abuse and HIV disease. Results of this study demonstrated that the side effect profile of naltrexone appears to be similar in both alcoholic and opioid dependent populations, and that serious side effects are uncommon.

In the clinical studies, treatment with naltrexone supported abstinence, prevented relapse and decreased alcohol consumption. In the uncontrolled study, the patterns of abstinence and relapse were similar to those observed in the controlled studies.

Naltrexone was not uniformly helpful to all patients, and the expected effect of the drug is a modest improvement in the outcome of conventional treatment.

iii. Add the following as the subsection immediately following the *Individualization of Dosage* subsection:

Treatment of Alcoholism: The placebo-controlled studies that demonstrated the efficacy of naltrexone as an adjunctive treatment of alcoholism used a dose regimen of naltrexone hydrochloride 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not studied in these trials.

Physicians are advised that 5 to 15% of patients taking naltrexone for alcoholism will complain of non-specific side effects, chiefly gastrointestinal upset. Prescribing physicians have tried using an initial 25 mg dose, splitting the daily dose, and adjusting the time of dosing with limited success. No dose or pattern of dosing has been shown to be more effective than any other in reducing these complaints for all patients.

iv. *Treatment of Narcotic Dependence*:, Last paragraph, first sentence -

... addict population and in initial clinical trials in alcoholism. Clinics ...

b. INDICATIONS AND USAGE

Naltrexone hydrochloride tablets are indicated in the treatment of alcohol dependence and for the blockade ...

c. WARNINGS

Revise the first sentence of the second paragraph following the WARNINGS box as follows:

... recommended for the treatment of alcoholism or opiate blockade ...

d. ADVERSE REACTIONS

i. Add the following text as the first paragraph:

During two randomized, double-blind, placebo-controlled 12 week trials to evaluate the efficacy of naltrexone as an adjunctive treatment of alcohol dependence, most patients tolerated naltrexone well. In these studies, a total of 93 patients received naltrexone hydrochloride at a dose of 50 mg once daily. Five of these patients discontinued naltrexone because of nausea. No serious adverse events were reported during these two trials.

ii. Reported Adverse Events, second sentence.

Studies in alcoholic populations and in volunteers ...

iii. Add the following text as the subsection immediately following "Reported Adverse Events":

Alcoholism:

In an open label safety study with approximately 570 individuals with alcoholism receiving naltrexone, the following new-onset adverse reactions occurred in 2% or more of the patients: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%).

Depression (5 to 7%), suicidal ideation (2%), and attempted suicide (<1%) have been reported in individuals on naltrexone, placebo and in concurrent control groups undergoing treatment for alcoholism. Although no causal relationship with naltrexone is suspected, physicians should be aware that treatment with naltrexone does not reduce the risk of suicide in these patients (see **PRECAUTIONS**).

e. DOSAGE AND ADMINISTRATION

i. Add the following as the first subsection after the first sentence:

Treatment of Alcoholism:

A dose of 50 mg once daily is recommended for most patients (see CLINICAL PHARMACOLOGY, Clinical Trials, Individualization of Dosage).
Naltrexone should be considered as only one of many factors determining the success of treatment of alcoholism. Factors associated with a good outcome in the clinical trials with naltrexone were the type, intensity, and duration of treatment; appropriate management of comorbid conditions; use of community-based support groups; and good medication compliance. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, especially medication compliance.

ii. Intravenous Challenge

"naloxone hydrochloride" rather than "naloxone" throughout this paragraph.

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.

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

October 13, 1997

N1

DRG AMENDMENT

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: **ANDA 74-918**
Naltrexone Hydrochloride Tablets, 50 mg
Amendment to a Pending Application

Reference is made to our pending Abbreviated New Drug Application dated *June 27, 1996* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Naltrexone Hydrochloride Tablets, USP 50 mg.**

Reference is also made to Barr's Major Amendment dated May 22, 1997 in response to the Agency's letter dated January 8, 1997:

The purpose of this Amendment is to correct a mistake in Barr's May 22, 1997 Major Amendment. In particular, Barr responded to comments 6g and 6i of the May 22, 1997 Major Amendment stating that Barr .or Naltrexone Hydrochloride Tablets, 50 mg finished product release and stability testing. Upon realizing the error, I telephoned Tim Ames, Project Manager, FDA and informed him that Barr has Mr. Ames informed me that Barr should amend the application with the correction and to include the associated documentation. Mr. Ames added that this amendment would not alter the Agency's review time. Therefore, Barr has revised the following documents to

RECEIVED

OCT 14 1997

GENERIC DRUG

- Quality Control Specification Test Record, Spec.: 0902 - Rev. 3 (see page 1 to 3);
- Acceptance Tests for In-Process and Finished Products TM-420C (see pages 4 to 31),
- Bioequivalence/Test Batch Stability Specification Test Record, Rev. 2 (see pages 32 to 34),
- Marketed Product Stability Specification Sheet/Test Record, Rev. 2 (see pages 35 to 37),
- Bioequivalence/Test Batch Stability Protocol (see pages 38 to 41),
- Marketed Stability Protocol (see pages 42 to 46).

Lastly, Barr revised its container label for the 30 count size to state, "Unit of Use". Barr revised its container label for the 30 count size to be in accordance with USP 23 supplement 6, General Notices and Requirements section, page 3641 concerning "unit of use container". The revised container label is found on page 47.

An identical copy of this Amendment has been provided to the New Jersey District Office. A document certification is attached. This completes the Amendment to Barr's pending application.

Sincerely,

Barr Laboratories, Inc.

Christine Mundkur
Regulatory Counsel and Director
of Regulatory Affairs

This submission is comprised of Pages 1 through 47.

CM:mw

Barr Laboratories, Inc.

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

July 14, 1997

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: **ANDA 74-918**
Naltrexone Hydrochloride Tablets, 50 mg
Gratis Amendment General Correspondence

Reference is made to our pending Abbreviated New Drug Application dated *June 27, 1996* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Naltrexone Hydrochloride Tablets, 50 mg.**

Reference is also made to the telephone conversation of July 11, 1997 between Mr. Tim Ames, FDA Project Manager, OGD, FDA and Claire M. Lathers, Ph.D., F.C.P., of Barr Laboratories, Inc.

Original ANDA 74-918 Naltrexone Hydrochloride Tablets, 50 mg contained a typographical error on page 09-00003 (Exhibit 1). Item I on this page indicated that:

> **I. <u>Actual Drug Manufacturing will be Performed at:</u>**
>
> The compounding, tabulating, packaging and labeling for this product will occur at:
>
> Barr Laboratories, Inc.
> 2 Quaker Road
> Pomona, New York 10970-0519.

continued . . . . . .

The corrected page (see revised page 1) states:

I. Actual Drug Manufacturing Will be Performed at:

The compounding and tableting and coating for this product will occur at:

Barr Laboratories, Inc
265 Livingston Street
Northvale, N.J. 07647-0008

II. Actual Packaging and Labeling Will be Performed at:

Barr Laboratories, Inc.
246 Pegasus Avenue
Northvale, N.J. 07647-0008

The remainder of the text on original ANDA page 09-00003 was correct.

Please note, as demonstrated on the executed manufacturing master (batch record) and packaging records (original ANDA pages 12-00005 to 12-00043), the submission bioequivalence batch for Naltrexone Hydrochloride Tablets, 50 mg was manufactured at Barr Laboratories, Inc., 265 Livingston Street, Northvale, New Jersey and packaged at Barr Laboratories 246 Pegasus Avenue, Northvale, New Jersey.

If you have any further questions or need additional information, please do not hesitate to call me at 914-362-2693.

Sincerely,

BARR LABORATORIES, INC.

Claire M. Lathers, Ph.D., F.C.P.
Chief Scientific Officer

CML:lls
Enclosure
This submission is comprised of **Page 1 and Exhibit 1.**

Barr Laboratories, Inc.

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

May 22, 1997

EPL

NDA ORIG AMENDMENT

N/AC

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: **ANDA 74-918**
Naltrexone Hydrochloride Tablets, 50 mg
Major Amendment to a Pending Application

Reference is made to our pending Abbreviated New Drug Application dated *June 27, 1996* submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Naltrexone Hydrochloride Tablets, 50 mg**.

The following response is to your letter dated *January 8, 1997* in which the following is stated:

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

COMMENT:

A. CHEMISTRY DEFICIENCIES

1. Regarding components and composition:

   a. Please revise and resubmit your components and composition statement to indicate the amount of [redacted] and Purified Water.

Pages PURGED CONTAIN TRADE SECRET AND CONFIDENTIAL COMMERCIAL INFORMATION

...continued

a. General

i. We encourage the use of "to" rather than a hyphen when expressing a range of numbers throughout your insert labeling.

ii. Use "naltrexone" rather than "naltrexone hydrochloride" or "naltrexone hydrochloride tablets" except in the following locations (use "naltrexone hydrochloride" in these locations) -

DESCRIPTION section
CLINICAL PHARMACOLOGY
-Pharmacodynamic actions
-Paragraph 1 (line 1)
-Paragraph 5
-Clinical Trials
-Treatment of Narcotic Dependence
-Paragraph 1 (line 1-2)
-Paragraph 2 (line 3)
-Paragraph 3 (line 4)
WARNINGS
-Hepatotoxicity
-Paragraph 2, first paragraph following boxed WARNINGS (line 3-4)
-Paragraph 3 (lines 3 and 10)
PRECAUTIONS
-Carcinogenesis, Mutagenesis Impairment of Fertility
(Impairment of Fertility) (line 1)
-Pregnancy (line 7 and 8)
ADVERSE REACTIONS
-Paragraph 1 (line 6-7)
-Paragraph 2 (line 6-7)
OVERDOSAGE
-line 3-4
DOSAGE AND ADMINISTRATION
-Treatment of Narcotic Dependence (guideline #3)
-Alternative Dosing Schedules, Paragraph

...continued

1 (lines 1-2 and 9)
HOW SUPPLIED section - Make no revision

iii. Use "naloxone", rather than "Narcan", throughout your insert labeling except where indicated otherwise below.

b. DESCRIPTION

i. Delete "NARCAN®",

ii. Include the chemical name of naltrexone hydrochloride.

iii. Provide the structural formula, molecular formula, and molecular weight for naltrexone hydrochloride rather than naltrexone.

iv. Delete the last sentence of paragraph 2 and revise the final paragraph as follows -

Each tablet, for oral administration, contains 50 mg of naltrexone hydrochloride. In addition, each tablet contains . . .

v. In your listing of inactive ingredients, correctly spell, "hydroxypropyl".

c. CLINICAL PHARMACOLOGY

i. Pharmacodynamic Actions

Make the following revision in the last sentence, ". . . reaction as a result of opioid use.".

ii. Make the following revision in the last line, ". . . see PRECAUTIONS: Information for Patients)".

d. INDICATIONS AND USAGE

i. Naltrexone hydrochloride tablets are indicated . . .

ii. Last sentence, ". . . for the addiction.", (singular).

...continued

e. CONTRAINDICATIONS

Make consistent use of the numbering format in this section, e.g., "1)" vs "1."

f. WARNINGS

i. Bold the text inside the boxed warning.

ii. Make the following revision in the first sentence of the penultimate paragraph, ". . . recommended for opiate blockade. . .".

iii. Make the following revision in the last sentence of this section, ". . . see PRECAUTIONS: Information for Patients)".

g. PRECAUTIONS

i. Information for Patients

a) Make the following revision in the first paragraph, ". . . with naltrexone:", (colon).

b) Second paragraph, first sentence:

You have been prescribed naltrexone hydrochloride tablets as part . . .

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

Revise so that this is consistent in format with other subsection heading. Carcinogenesis, Mutagenesis, Impairment of Fertility are subsections of this subsection and should be revised in format as appropriate.

h. ADVERSE REACTIONS

i. Delete the first paragraph.

ii. New first paragraph, last sentence, ". . . see WARNINGS AND PRECAUTIONS. . .".

...continued

iii. New fourth paragraph, last sentence, ". . . WARNINGS, AND DOSAGE AND . . .".

iv. Reported Adverse Events

a) Second sentence:

Studies in volunteers in clinical pharmacology studies. . .

b) Last sentence, ". . .see CLINICAL PHARMACOLOGY, Clinical Trials, *Individualization*. . .".

i. DOSAGE AND ADMINISTRATION

i. Initiate treatment with Naltrexone using the following guidelines:

In the Intravenous Challenge subsection, revise "NARCAN" to read "naloxone hydrochloride", rather than "naloxone".

ii. Alternative Dosing Schedules:

Make the following revision in the second paragraph, ". . . WARNINGS AND CLINICAL PHARMACOLOGY, Clinical Trials, *Individualization of Dosage*. . .".

j. HOW SUPPLIED

i. In physical descriptions of your tablet submitted in this application, the debossed "50" appears above the score. If this is how your tablet appears, revise the tablet description in this section as follows, "50/902", rather than "902/50",

ii. Add the statement, "Protect from light" to be consistent with the labeling of the listed drug.

Please prepare and submit final print container labels and package insert labeling.

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 land explained.

...continued

RESPONSE:

Barr revised its container labels and package brochure to incorporate the changes in your comments. We are submitting final printed container labels and package brochure on pages 178 and 179. Also included is a side-by-side of our proposed labeling with our last submission (see pages 181 to 203).

Please note that Barr is now submitting an additional package size of 50's. Barr is submitting the proposed Packaging Master for the 50 count package configuration. The 50's size is the same container/closure system as the 30's and 100's. Therefore, the 50's package size is bracketed by the 30's and 100's container/closure systems and their respective stability data.

COMMENT:

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

RESPONSE:

Your comment is acknowledged.

COMMENT:

In addition to responding to these deficiencies, please note that the samples of the drug substance, finished product, and impurity/degradant standards will be requested by an FDA representative for methods validation.

RESPONSE:

Your comment is acknowledged.

...continued

COMMENT:

Regarding Synthesis:

These deficiencies must be corrected before the subject ANDA can be approved.

RESPONSE:

COMMENT:

Please be advised that the stability data must be submitted on three production batches in order to extend the expiration dating period post approval.

RESPONSE:

Your comment is acknowledged.

...continued

REFERENCE: **ANDA 74-918**
Naltrexone Hydrochloride Tablets, 50 mg

An identical copy of this Amendment has been provided to the New Jersey District Office. A document certification is attached. This completes the present response to the Agency's deficiency letter dated *January 8, 1997.*

Sincerely,

Barr Laboratories, Inc.

Christine Mundkur for

Claire M. Lathers, Ph.D., F.C.P.
Chief Scientific Officer

This submission is comprised of **Pages 1 through 203 and Exhibits 1 through 12.**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-918

Barr Laboratories, Inc.
Attention: Christine A. Mundkur
2 Quaker Road
Pomona, NY 10970-0519

JAN 8 1997

Dear Sir:

This is in reference to your abbreviated new drug application dated June 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naltrexone Hydrochloride Tablets, 50 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding components and composition:

   a. Please revise and resubmit your components and composition statement to indicate the amount of nd Purified Water.

   b. Please revise and resubmit your components and composition statement to reflect the film components and weights, etc.

2. Regarding raw materials:

   a. Please update Barr's COA for Naltrexone Hydrochloride to include identification test nd the test results.

   b. Please update Barr's COA for Naltrexone Hydrochloride to provide limits and resubmit.

   c. Please provide nd results on your drug substance.

   d. Please provide total in your COA for and resubmit.

e. The color additive shall conform in identity and specifications to the requirements of 21 CFR 73.1200. Please submit FDA color additive certificate supplied by vendor certifying compliance with 21 CFR.

3. Regarding other ingredients:

Please provide the function of the alternate analytical laboratories and the tests performed by each laboratory in the other firms Section.

4. Regarding manufacturing and processing:

a. In your blank production and executed batch records the tablet description is not provided In the description section of your finished product and stability specifications and stability reports showed that tablets are debossed. Please resubmit corrected copies.

b. Please submit the and include in your batch records.

5. Regarding container/closures:

a. Please provide a DMF authorization letter for

b. Please provide application and removal torque limits (33/400 mm closures) for the container closure system.

c. According to your container labeling this product should be dispensed in tight, light resistant containers. Please note that USP <671> permeation test results for tight container/closure systems should be submitted by Barr Laboratories or

6. Regarding laboratory controls:

a. The limits for percent yield of film coated tablets in Section 1 and Section 2 were and . Please explain why your net percent yields do not meet these limits.

b. Please provide a thickness range for film coated tablets.

c. Finished product
.ıdividual and average) should be provided for both finished and

d. Please provide labeling reconciliation limit.

e. Please provide the above specifications in your executed and blank batch records.

f. Please note that deleting in-process test methods and specifications will require the submission of supplements.

g. Please provide actual limits for
.nstead of "report results" in finished product specifications and resubmit.

h. In finished product release and stability specifications, the color of the tablet was described as Beige. Please clarify how you can have Beige color tablets using
.n the formulation. Please clarify.

i. The moisture content method and limit should be included in your finished product and stability protocol.

j. Please include degradation products and impurity limits in drug substance, finished product and stability protocol

8. Regarding methods:

a. Drug substance:

Since Naltrexone HCl is sensitive to light, the test results under intense light (or UV light) should also be included in your forced degradation studies. The relevant chromatograms and % recovery test results should be provided.

b. Finished product:

c.

d.

9. Regarding stability:

a. Please note control room temperature storage conditions should be performed under ambient relative humidity and it should be indicated in your stability reports.

b. Please revise your marketed product stability protocol for accelerated conditions as samples will be tested initially, 1, 2, and 3 months.

c. Please revise your post-approval commitment as follows: The stability report results should be submitted in the next annual report.

d. Please indicate the manufacturing site in your stability reports.

e. Please revise the related substances limits for a single impurity and total impurities in your stability testing specifications to be consistent with your finished product release specifications and resubmit.

f. Please revise the n your stability protocol and reports and resubmit.

B. LABELING DEFICIENCIES

1. CONTAINER (30s, 100s)

Add the following statement to your container label, "Protect from light.".

2. INSERT

a. General

i. We encourage the use of "to" rather than a hyphen when expressing a range of numbers throughout your insert labeling.

ii. Use "naltrexone" rather than "naltrexone hydrochloride" or "naltrexone hydrochloride tablets" except in the following locations (use "naltrexone hydrochloride" in these locations) -

DESCRIPTION section
CLINICAL PHARMACOLOGY
-Pharmacodynamic actions
-Paragraph 1 (line 1)
-Paragraph 5
-Clinical Trials
-Treatment of Narcotic Dependence
-Paragraph 1 (line 1-2)
-Paragraph 2 (line 3)
-Paragraph 3 (line 4)
WARNINGS
-Hepatotoxicity
-Paragraph 2, first paragraph following boxed WARNINGS (line 3-4)
-Paragraph 3 (lines 3 and 10)

PRECAUTIONS
-Carcinogenesis, Mutagenesis Impairment of Fertility
(Impairment of Fertility) (line 1)
-Pregnancy (line 7 and 8)
ADVERSE REACTIONS
-Paragraph 1 (line 6-7)
-Paragraph 2 (line 6-7)
OVERDOSAGE
-line 3-4

DOSAGE AND ADMINISTRATION
-Treatment of Narcotic Dependence (guideline #3)
-Alternative Dosing Schedules, Paragraph 1 (lines 1-2 and 9)
HOW SUPPLIED section - Make no revision

iii. Use "naloxone", rather than "Narcan", throughout your insert labeling except where indicated otherwise below.

b. DESCRIPTION

i. Delete "NARCAN®".

ii. Include the chemical name of naltrexone hydrochloride.

iii. Provide the structural formula, molecular formula, and molecular weight for naltrexone hydrochloride rather than naltrexone.

iv. Delete the last sentence of paragraph 2 and revise the final paragraph as follows -

Each tablet, for oral administration, contains 50 mg of naltrexone hydrochloride. In addition, each tablet contains...

v. In your listing of inactive ingredients, correctly spell, "hydroxypropyl".

c. CLINICAL PHARMACOLOGY

i. Pharmacodynamic Actions

Make the following revision in the last sentence, "...reaction as a result of opioid use.".

ii. Make the following revision in the last line, "...see PRECAUTIONS: Information for Patients).".

d. INDICATIONS AND USAGE

i. Naltrexone hydrochloride tablets are indicated...

ii. Last sentence, "...for the addiction.", (singular).

e. CONTRAINDICATIONS

Make consistent use of the numbering format in this section, e.g., "1)" vs "1.".

f. WARNINGS

i. Bold the text inside the boxed warning.

ii. Make the following revision in the first sentence of the penultimate paragraph, "...recommended for opiate blockade...".

iii. Make the following revision in the last sentence of this section, "...see PRECAUTIONS: Information for Patients)".

g. PRECAUTIONS

i. Information for Patients

a) Make the following revision in the first paragraph, "...with naltrexone:", (colon).

b) Second paragraph, first sentence:

You have been prescribed naltrexone hydrochloride tablets as part...

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

Revise so that this is consistent in format with other subsection headings. Carcinogenesis, Mutagenesis, Impairment of Fertility are subsections of this subsection and should be revised in format as appropriate.

h. ADVERSE REACTIONS

i. Delete the first paragraph.

ii. New first paragraph, last sentence, "...see WARNINGS and PRECAUTIONS...".

iii. New fourth paragraph, last sentence, "...WARNINGS, and DOSAGE AND...".

iv. Reported Adverse Events

a) Second sentence:

Studies in volunteers in clinical pharmacology studies...

b) Last sentence, "...see CLINICAL PHARMACOLOGY, Clinical Trials, *Individualization*...".

i. DOSAGE AND ADMINISTRATION

i. Initiate treatment with Naltrexone using the following guidelines:

In the Intravenous Challenge subsection, revise "NARCAN" to read "naloxone hydrochloride", rather than "naloxone".

ii. Alternative Dosing Schedules:

Make the following revision in the second paragraph, "...WARNINGS and CLINICAL PHARMACOLOGY, Clinical Trials, *Individualization of Dosage*...".

j. HOW SUPPLIED

i. In physical descriptions of your tablet submitted in this application, the debossed "50" appears above the score. If this is how your tablet appears, revise the tablet description in this section as follows, "50/902", rather than "902/50".

ii. Add the statement, "Protect from light" to be consistent with the labeling of the listed drug.

Please prepare and submit final print container labels and package insert labeling.

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.

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

In addition to responding to these deficiencies, please note that the samples of the drug substance, finished product, and impurity/degradant standards will be requested by an FDA representative for methods validation.

Regarding Synthesis:

holder. These deficiencies must be corrected before the subject ANDA can be approved.

Please be advised that the stability data must be submitted on three production batches in order to extend the expiration dating period post approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
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

June 27, 1996

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 Naltrexone Hydrochloride Tablets, 50 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 seven 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 five volumes. The bioequivalence part of the review copy is contained in orange binders and consists of five volumes.

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 Cheesemore (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.

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 New Jersey District Office.

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

Sincerely

BARR LABORATORIES, INC.

Christine A. Mundkur
Associate Counsel

CAM:mw
Enclosures

ANDA 74-918

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

AUG 9 1996

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: Naltrexone Hydrochloride Tablets, 50 mg

DATE OF APPLICATION: June 27, 1996

DATE OF RECEIPT: June 28, 1996

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) 594-0305

Sincerely yours,

8/9/96

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