CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74862

CORRESPONDENCE

AB Generics L.P.

100 CONNECTICUT AVENUE, NORWALK, CT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

BIOAVAILABILITY

March 11, 1996

14-862

SUBMITTED IN SINGLE COPY
GENERAL CORRESPONDENCE

Charles J. Ganley, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
7500 Standish Place, HFD-650
Rockville, MD 20855

Desk Copy with Diskette
Mr. Lawrence Galvin

N/A

Re: Morphine Sulfate Controlled-Release 30 mg Tablets
ANDA # Not Yet Assigned

Dear Dr. Ganley:

Reference is made to the above Abbreviated New Drug Application submitted on February 23, 1996.

Enclosed is a diskette and paper copy for the bioequivalence study MO94-1103.

Should you have any questions, please contact me at the telephone number below.

Sincerely yours,

James H. Conover, Ph.D.
Executive Director
Drug Regulatory Affairs & Compliance
Tel: (203) 854-7280

JC:kh
Enclosures

RECEIVED
MAR 14 1996
GENERIC DRUGS

g:\sharedpt\dra\mat\msabg\anda\30mg\datadisk.doc

AB Generics L.P.

100 CONNECTICUT AVENUE, NORWALK, CT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

March 11, 1996

NEW CORRES

ABBREVIATED NEW DRUG APPLICATION

Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Charles J. Ganley, M.D.

Desk Copies:
Dr. Charles J. Ganley (letter only)
Ms. Heather Pedersen, Newark District Office - Field Review Copy
Mr. Lawrence Galvin - Diskette and Paper Copy of Study Data

Re: Morphine Sulfate Controlled-Release 60 mg Tablets

Dear Dr. Ganley:

We hereby submit an Abbreviated New Drug Application (ANDA) for the subject morphine prescription drug product in accordance with the statutory provisions at section 505 (j) of the Act [21 U.S.C. §355 (j)]. This submission is an original application following the content and format of 21 CFR §314.50 as directed by the Abbreviated New Drug Regulations final rule published on April 28, 1992 in the Federal Register.

The subject ANDA is a drug product that is the "same" as a drug product [MS Contin® 60 mg (controlled-release) Tablets] listed in the approved drug product list published by the FDA with respect to active ingredient, route of administration, dosage form, strength, and conditions of use recommended in the labeling. MS Contin® 60 mg (controlled-release) Tablets is the marketed reference product for this application.

In addition to the archival set of six (6) volumes, we are also providing separately bound copies for each technical reviewer's section in this submission.

We also certify that a complete and accurate chemistry, manufacturing and controls technical section identical to that presented in this submitted ANDA will be provided as a field copy to Ms. Heather Pedersen, Newark District Office.

Additional Information:

AB Generics L.P. is a new generic company associated with The Purdue Frederick Company. It is our intention to file an ANDA for each of the currently marketed strengths of morphine sulfate products, designated as MS Contin® 15, 30, 60, 100 & 200 mg (controlled-release) Tablets. MS Contin® products were filed by Purdue Frederick in NDA #19-516. ANDA's were filed by AB Generics L.P. for Morphine Sulfate Controlled-Release 200 mg Tablets on October 16, 1995, Morphine Sulfate Controlled-Release 100 mg Tablets on February 16, 1996 and Morphine Sulfate Controlled-Release 30 mg Tablets on February 23, 1996. Thus, this 60 mg ANDA is the fourth of five separate ANDA's to be submitted, as each strength requires both chemistry and manufacturing, as well as bioequivalence information to be considered by FDA in order to gain approval.

AB Generics L.P. will use (b)(4)(CC) as its manufacturer. (b)(4)(CC) personnel facilities and location (b)(4)(CC) are identical to those of the P.F. Laboratories which is the manufacturer for Purdue Frederick. Therefore, the same manufacturing facilities, personnel, equipment, testing methods, controls, packaging, drug ingredients, as well as container/closure materials will be used in the manufacture of the generic line as is currently used for the MS Contin® Tablets product line. In addition, the same vendors will be used as those approved for The Purdue Frederick product line.

AB Generics L.P. intends to manufacture the generic product strengths of each of these controlled-release morphine sulfate products according to the approved Purdue Frederick formulation, except that a color (titanium dioxide) will be added to each of the formulations of the AB Generics L.P. products.

References:

Please see attached references of correspondence between AB Generics L.P. and FDA Generic Drug Division dated as follows:

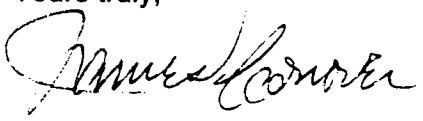
May 20, 1993	Initial query by AB Generics L.P.
July 1, 1993	Office of Generic Drugs reply
February 17, 1994	Office of Generic Drugs clarification of Bioequivalence requirements
September 30, 1994	Office of Generic Drugs comments on Bioequivalence protocols submitted for review
November 30, 1994	Office of Generic Drugs comments on Bioequivalence requirements (revised from 2/17/94)

Bioequivalence Study Data:

Also attached is a diskette (in archive copy *only*) and paper copy for bioequivalence study MO94-1003.

Please contact me if you have any additional comments or questions regarding this submission.

Yours truly,



James H. Conover, Ph.D.
Executive Director
Drug Regulatory Affairs & Compliance
Telephone: (203) 854-7280

JHC:kh
Enclosure

ANDA 74-862

AB Generics, L.P.
Attention: James H. Conover, Ph.D.
100 Connecticut Avenue
Norwalk, CT 06850-3590

3 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated February 23, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Morphine Sulfate Controlled-release Tablets, 30 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> You have failed to provide packaging records for your blister packaging. Also, please explain the reason your stability data for the blister package has a different lot number than that of your test batch. Please be aware that data generated for approval of the application must use the dedicated test batch.
>
> You have failed to clearly designate which supplier of the active ingredient was used in the production of your test batch. Please be aware that if approval is sought for an additional source of the new drug substance you are expected to include the data from a test batch that yields at least 10% of the number of finished dosage units proposed in the maximum size production batch for which authorization is sought or 100,000 finished dosage units whichever is greater.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In future submissions, please be advised that providing information in the appropriate sections of the application instead of numerous appendices assists the reviewer in reviewing your submission.

In addition, while we note that you have provided a debarment certification and list of convictions, you failed to provide this certification with an original signature. Please be aware that certifications requiring original signatures should be included in the **archival copy** of the application. Please provide this certification with an original signature.

We also note that you list (b)(4)(CC) as a supplier of your active ingredient and provide a authorization to access their Drug Master File (DMF), you have failed to produce a test batch and perform necessary studies using the (b)(4)(CC) product. Please be aware that authorization to use alternate suppliers cannot be given without the appropriate information submitted to the application. Please refer to the Office of Generic Drugs, Policy and Procedure Guide # 22-90.

Although you provide information regarding the field copy of the application in your cover letter, your must certify that the third (field) copy of the application is a "true" copy of the technical sections of the application and that this copy has been sent to the district office. Please provide this revised certification with an original signature.

You have failed to provide labeling for your blister packaging. Please provide four draft copies of the package labeling (container labels and package insert) for this packaging configuration and a side-by-side comparison with your proposed labeling and the approved labeling of the reference listed drug with all differences annotated and explained. In addition, while we note you provided a comparison of your proposed package insert with the approved insert of the reference listed drug, please be aware that labeling is defined as package labels for all containers as well as the package insert. Please provide a side-by-side comparison of your proposed package labeling with the approved labeling of the reference listed drug with all differences annotated and explained [21 CFR 314.94(a)(8)(iv)].

Also, in the interim, please submit three additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the sample (both the bulk active ingredient and the finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Project Manager
(301) 594-0315

Sincerely yours,

/S/ [redacted] 3/18/96

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

ANDA 74-862
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett
Endorsement: HFD-615/PRickman, Ac /S/ [redacted] 3/15/96 date
HFD-615/WRussell, CS [redacted] date
HFD-623/Chem Branch [redacted] 3.15.96
X:\new\firmsnz\abgenerics\ltrs&rev\74-862
F/T bcw/3-13-96
ANDA Refuse to File!

AB Generics L.P.
100 CONNECTICUT AVENUE, NORWALK, CT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

February 23, 1996

ABBREVIATED NEW DRUG APPLICATION

Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Charles J. Ganley, M.D.

Desk Copies:
Dr. Charles J. Ganley (letter only)
Ms. Heather Pedersen, Newark
District Office - Field Review Copy

Re: Morphine Sulfate Controlled-Release 30 mg Tablets

Dear Dr. Ganley:

We hereby submit an Abbreviated New Drug Application (ANDA) for the subject morphine prescription drug product in accordance with the statutory provisions at section 505 (j) of the Act [21 U.S.C. §355 (j)]. This submission is an original application following the content and format of 21 CFR §314.50 as directed by the Abbreviated New Drug Regulations final rule published on April 28, 1992 in the Federal Register.

The subject ANDA is a drug product that is the "same" as a drug product [MS Contin® 30 mg (controlled-release) Tablets] listed in the approved drug product list published by the FDA with respect to active ingredient, route of administration, dosage form, strength, and conditions of use recommended in the labeling. MS Contin® 30 mg (controlled-release) Tablets is the marketed reference product for this application.

In addition to the archival set of seven (7) volumes, we are also providing separately bound copies for each technical reviewer's section in this submission.

We also certify that a complete and accurate chemistry, manufacturing and controls technical section identical to that presented in this submitted ANDA will be provided as a field copy to Ms. Heather Pedersen, Newark District Office.

Additional Information:

AB Generics L.P. is a new generic company associated with The Purdue Frederick Company. It is our intention to file an ANDA for each of the currently marketed strengths of morphine sulfate products, designated as MS Contin® 15, 30, 60, 100 & 200 mg (controlled-release) Tablets. MS Contin® products were filed by Purdue Frederick in NDA #19-516. ANDA's were filed by AB Generics L.P. for Morphine Sulfate Controlled-Release 200 mg Tablets on October 16, 1995 and for Morphine Sulfate Controlled-Release 100 mg Tablets on February 16, 1996. Thus, this 30 mg ANDA is the third of five separate ANDA's to be submitted, as each strength requires both chemistry and manufacturing, as well as bioequivalence information to be considered by FDA in order to gain approval.

AB Generics L.P. will use (b)(4)(CC) as its manufacturer. (b)(4)(CC) personnel facilities and location (b)(4)(CC), are identical to those of the P.F. Laboratories which is the manufacturer for Purdue Frederick. Therefore, the same manufacturing facilities, personnel, equipment, testing methods, controls, packaging, drug ingredients, as well as container/closure materials will be used in the manufacture of the generic line as is currently used for the MS Contin® Tablets product line. In addition, the same vendors will be used as those approved for The Purdue Frederick product line.

AB Generics L.P. intends to manufacture the generic product strengths of each of these controlled-release morphine sulfate products according to the approved Purdue Frederick formulation, except that a color (titanium dioxide) will be added to each of the formulations of the AB Generics L.P. products.

References:

Please see attached references of correspondence between AB Generics L.P. and FDA Generic Drug Division dated as follows:

May 20, 1993	Initial query by AB Generics L.P.
July 1, 1993	Office of Generic Drugs reply
February 17, 1994	Office of Generic Drugs clarification of Bioequivalence requirements
September 30, 1994	Office of Generic Drugs comments on Bioequivalence protocols submitted for review
November 30, 1994	Office of Generic Drugs comments on Bioequivalence requirements (revised from 2/17/94)

Please contact me if you have any additional comments or questions regarding this submission.

Yours truly,

James H. Conover KH

James H. Conover, Ph.D.
Executive Director
Drug Regulatory Affairs & Compliance
Telephone: (203) 854-7280

JHC:kh
Enclosure

AB Generics L.P.

100 CONNECTICUT AVENUE, NORWALK, CT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

May 3, 1996 BIOAVAILABILITY

NDA ORIG AMENDMENT MAC **ABBREVIATED NEW DRUG APPLICATION SUPPLEMENT**

Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857-2773

Attn: Mr. Douglas A. Sporn

Desk Copies:
Ms. Heather Pedersen, *Newark District Office - Field Review Copy*
Mr. William Russell (letter only)

RECEIVED
MAY 09 1996
GENERIC DR.

Re: Morphine Sulfate Controlled-Release 15 mg Tablets
Supplement to ANDA # 74-862

Dear Mr. Sporn:

We hereby submit an Abbreviated New Drug Application (ANDA) Supplement for the subject morphine prescription drug product in accordance with the statutory provisions at section 505 (j) of the Act [21 U.S.C. §355 (j)]. This submission is an original application following the content and format of 21 CFR §314.50 as directed by the Abbreviated New Drug Regulations final rule published on April 28, 1992 in the Federal Register.

The subject ANDA is a drug product that is the "same" as a drug product [MS Contin® 15 mg (controlled-release) Tablets] listed in the approved drug product list published by the FDA with respect to active ingredient, route of administration, dosage form, strength, and conditions of use recommended in the labeling. MS Contin® 15 mg (controlled-release) Tablets is the marketed reference product for this application.

In addition to the archival set of six (6) volumes, we are also providing separately bound copies for each technical reviewer's section in this submission.

We also certify that a complete and accurate chemistry, manufacturing and controls technical section identical to that presented in this submitted ANDA supplement has been sent as a field copy to Ms. Heather Pedersen, Newark District Office.

Additional Information:

AB Generics L.P. is a new generic company associated with The Purdue Frederick Company. It is our intention to file an ANDA or ANDA supplement for each of the currently marketed strengths of morphine sulfate products, designated as MS Contin® 15, 30, 60, 100 & 200 mg (controlled-release) Tablets. MS Contin® products were filed by Purdue Frederick in NDA #19-516. The 100 and 200 mg tablet strengths of morphine sulfate controlled-release tablets have been grouped under ANDA #74-869. This ANDA supplement for

Morphine Sulfate Controlled-Release Tablets 15 mg is the last of the remaining three (3) tablet strengths to be submitted under ANDA #74-862 which currently includes the 30 and 60 mg tablet strengths. Each submission for each strength includes the chemistry and manufacturing, as well as bioequivalence information required by FDA in order to gain approval.

AB Generics L.P. will use (b)(4)(CC) as its manufacturer. (b)(4)(CC) personne, facilities and location (b)(4)(CC) are identical to those of the P.F. Laboratories which is the manufacturer for Purdue Frederick. Therefore, the same manufacturing facilities, personnel, equipment, testing methods, controls, packaging, drug ingredients, as well as container/closure materials will be used in the manufacture of the generic line as is currently used for the MS Contin® Tablets product line. In addition, the same vendors will be used as those approved for The Purdue Frederick product line.

AB Generics L.P. intends to manufacture the generic product strengths of each of these controlled-release morphine sulfate products according to the approved Purdue Frederick formulation, except that a color (titanium dioxide) will be added to each of the formulations of the AB Generics L.P. products.

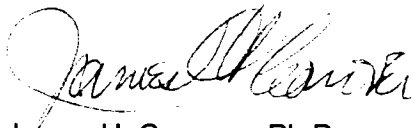
References:

Please see attached references of correspondence between AB Generics L.P. and FDA Generic Drug Division dated as follows:

May 20, 1993	Initial query by AB Generics L.P.
July 1, 1993	Office of Generic Drugs reply
February 17, 1994	Office of Generic Drugs clarification of Bioequivalence requirements
September 30, 1994	Office of Generic Drugs comments on Bioequivalence protocols submitted for review
November 30, 1994	Office of Generic Drugs comments on Bioequivalence requirements (revised from 2/17/94)

Please contact me if you have any additional comments or questions regarding this submission.

Yours truly,



James H. Conover, Ph.D.
Executive Director
Drug Regulatory Affairs & Compliance
Telephone: (203) 854-7280

JHC:kh
Enclosure

ANDA 74-862

AB Generics, L.P.
Attention: James H. Conover, Ph.D.
100 Connecticut Avenue
Norwalk, CT 06850-3590

APR 24 1996

Dear Sir:

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 also made to your correspondence dated March 11, 1996, our "Refuse to File" letter dated March 18, 1996, and your amendment dated April 2, 1996.

NAME OF DRUG: Morphine Sulfate Controlled-release Tablets, 30 mg and 60 mg

DATE OF APPLICATION: February 23, 1996

DATE OF RECEIPT: February 26, 1996

DATE ACCEPTABLE FOR FILING: April 3, 1996

We also acknowledge receipt of your submission for Morphine Sulfate Controlled-release Tablets, 60 mg, dated March 11, 1996 which was incorporated into your existing ANDA 74-862.

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:

Timothy Ames
Project Manager
(301) 594-1841

Sincerely yours,

/S/ [redacted] 4/24/96

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

ANDA 74-862
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief /S/ [redacted] 4/16/96 date
HFD-615/WRussell, CSO [redacted] date
HFD-647/JSimmons, Sup [redacted] 4.16.96 date
File\x:\new\firmsam\abgeneri\ltrs&rev\74862ac.f
F/T hrw 4-12-96
ANDA Acknowledgement Letter!

AB Generics L.P.

100 CONNECTICUT AVENUE, NORWALK, CT 06850-3590 • (203) 853-0123 FAX (203) 838-1576

VIA OVERNIGHT MAIL
EARLY DELIVERY

APR 0 3 1996

April 2, 1996

AMENDMENT TO PENDING APPLICATION

Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attn: Charles J. Ganley, M.D.

Desk Copies:
Dr. Charles J. Ganley (letter only)
Ms. Heather Pedersen, Newark
District Office - Field Review Copy
Mr. Jerry Phillips (letter only)
Mr. William Russell (letter only)

Re: Morphine Sulfate Controlled-Release 30 mg Tablets
ANDA #74-862

Dear Dr. Ganley:

Reference is made to our Abbreviated New Drug Application dated February 23, 1996 and the Agency's correspondence dated March 18, 1996 (Attachment #1). Please note that we have numbered the paragraphs of the attached copy of the Agency's letter to correspond with the numbered responses (outlined below) for ease of review.

In response to the following refusal to file issues under 21 CFR §314.101 (d) (3), outlined by the Agency in the attached March 18, 1996 correspondence, we provide the following information:

1. Blister Packaging

The 30 mg submission contains stability data and packaging records for blister packaging of the product, but labels/labeling are not provided.

We hereby withdraw the blister format for consideration of approval in the subject ANDA. It is our routine to run stability programs in bottle and blister containers, but there is no intention to market the blister format, and therefore no labels are provided in the applications, nor are any references made in the accompanying package inserts.

2. Active Ingredients Suppliers

In the subject ANDA, two (2) suppliers of active ingredient (morphine sulfate) were listed: (b)(4)(CC) We hereby withdraw (b)(4)(CC) as a supplier of the morphine active ingredient.

The stability results for product made with the (b)(4)(CC) supplied active ingredient are present in the subject ANDA, as are the Certificate of Analysis from the (b)(4)(CC) lot and the executed batch record. I will present the location of these items in the subject ANDA. A version of what follows exists in Section VIII.1.3 of the package (Volume 6, pg. 6).

- **Batch Record -** Volume 6, Appendix 6, page 170
  Notation of morphine sulfate ingredient code number in Raw Material # column. The code number refers to the P.F. Laboratories COA of the (b)(4)(CC) lot (Appendix 1, pg. 16). Immediately following the P.F. Laboratories COA is the laboratory assay report that ties the (b)(4)(CC) lot of morphine to the COA of P.F. Laboratories with the code number.

- **COAs -** (b)(4)(CC) (for morphine sulfate); Volume 6, Appendix 1, pg. 15.
  P.F. Laboratories (for morphine sulfate); Volume 6, Appendix 1, pg. 16.

- **Physical and Chemical Characteristics -** See Table of Contents for Appendix 1, Volume 6, page 12-35.

In addition, we hereby submit the following re-ordered documentation which does *not* contain any new information:

1. Pursuant to the request of Mr. Jerry Phillips in the attached letter, enclosed are replacement copies of Volume 6 and Volume 7 (Archival and Chemistry Section copies) which now contain the appendices within the sections to which they pertain. As such, there is no longer a a separate section containing only appendices in Volume 7. [Ten (10) additional copies of the newly revised global table of contents are also submitted reflecting the changes in Volumes 6 and 7. These copies are for insertion into the Archival Copy and Chemistry Copy, Volume 1 through Volume 5.] In addtion, three (3) copies (one for the Chemistry Copy, one for the Pharmacokinetic Copy and one for the Archival Copy) of pages 4R and 6R are provided to replace pages 4 and 6 in Volume 1 in order to correct the references to these appendices.
2. The Debarment Statement for AB Generics L.P. located in Volume 7, page 283 is provided with an original signature.
3. In response to the issue of (b)(4)(CC) listed as a supplier of the active ingredient, please see Item 2: *Active Ingredient Suppliers* from the first section under responses to the refusal to file issues.

4. We certify that a true copy of the technical section (as enclosed) **has been sent** as a field review copy to Ms. Heather Pedersen, Newark District Office.

5. **Labeling**

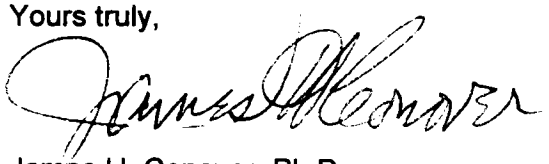
   a) In response to the issue of the blister packaging not being included in the labeling, please see Item 1: *Blister Packaging* from the first section under responses to the refusal to file issues.

   b) Pursuant to 21 CFR §314.50 (e) (2) (ii) and the request of Mr. William Russell, enclosed are eight (8) copies of the annotated side-by-side package insert (four for the Archival Copy and four for the Chemistry Copy). These copies have been revised to include both the reference listed drug and Morphine Sulfate Controlled-Release 30 mg Tablets.

6. Pursuant to 21 CFR §314.50 (e) (2) (I), enclosed are three (3) copies of the methods validation package.

Please contact me if you have any additional comments or questions regarding this submission.

Yours truly,



James H. Conover, Ph.D.
Executive Director
Drug Regulatory Affairs & Compliance
Telephone: (203) 854-7280

JHC:kh
Enclosures

2.1

ANDA 74-862

JUL 31 1996

A.B. Generics L.P.
Attention: James H. Conover, Ph.D.
100 Connecticut Avenue
Norwalk CT 06850-3590

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on February 23, 1996 and your amendment dated March 11, 1996, for Morphine Sulfate Controlled-release Tablets 30 mg and 60 mg.

The Office acknowledges the receipt of your amendments dated April 2, and May 3, 1996, which will be reviewed according to Agency policy. However the bioequivalence data submitted March 11, 1996 has been reviewed and the following comments are provided for your consideration:

1. The following comments apply to both the #MO94-1103, Morphine Sulfate Controlled-release Tablets 30 mg and #MO94-1003 Morphine Sulfate Controlled-release Tablets 60 mg studies:

   a. The potency and content uniformity for the test and reference products is required for review.

   b. The analytical raw data for all subjects in the studies was not submitted.

   c. The following pharmacokinetic parameters should be submitted for morphine and morphine-6-glucuronide, AUC_{0-t} (area under the plasma concentration-time curve from time zero to time t, calculated by the trapezoidal rule, where t is the last measurable time point) and AUC_{0-inf} (where $AUC_{0-inf} = AUC_t + C_t/Kel$, C_t is the last measurable drug concentration and Kel is the terminal elimination rate constant calculated according to an appropriate method).

   d. A 3.5" Diskettes in ASCII format containing the pharmacokinetic data for both Morphine and Morphine-6-Glucuronide data should be submitted to facilitate the review of this application.

   e. The dissolution testing data on Morphine Sulfate Controlled-release Tablets 30 mg and 60 mg in Simulated Gastric Fluid and on its Morphine Sulfate

Controlled-Release 200 mg and 100 mg Tablets in water. The dissolution method or methodology in which you plan to use along with the proposed dissolution specification should be submitted.

2. The following comments apply to the #MO94-1103, Morphine Sulfate Controlled-release Tablets 30 mg study:

   a. The representative (b)(4)(CC) submitted for subjects (#2, #12, #18, #19 and #21) are not legible. Please resubmit clear copies.

   b. In the study report section, it is stated that "Drug administration occurred at 0800 hours on study Day 1 and 8 (Phase 1 and Phase 2, respectively)". Table 4A (page 92) indicated that the subjects were dosed on different days. The dosing dates are as following:

Subjects No.	Phase I Date	Phase II Date
22, 23, 24, 25	12/12/94	12/19/94
2	12/12/94	12/20/94
16,17, 19, 21	12/13/94	12/19/94
1, 3, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 18, 20, 26	12/13/94	12/20/94

   Please explain these discrepancies.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

4.1

ANDA 74-862

AB Generics L.P.
Attention: James H. Conover, Ph.D.
100 Connecticut Avenue
Norwalk, CT 06856-3590

NOV 8 1996

Dear Dr. Conover:

This is in reference to your abbreviated new drug application dated February 23, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg and 60 mg.

Reference is also made to your amendments dated March 11, April 2, and May 3, 1996.

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

A. Chemistry Deficiencies

CHEMISTRY DEFICIENCIES

Pgs 1 - 7

published in the Federal Register on September 22, 1994.

d. In your stability testing requirements:

i. Please revise the dosage description section to indicate imprint instead of "indicia".

ii. Please revise and resubmit a tighter hardness limit.

iii. Please revise to include related substances test and limits for product in blister packages in your stability testing specifications and resubmit.

e. Please revise the description, hardness and related substances limits in your stability protocol and reports and resubmit.

B. Labeling Deficiencies

1. GENERAL COMMENT:

Revise the established name on all labels and labeling to read as follows:

Morphine Sulfate Extended-release Tablets

2. CONTAINER

a. See general comment.

b. Please note that there is no regulatory requirement for the listing of inactive ingredients on the container labels for solid oral dosage forms of prescription drug products. You may delete this information.

c. We encourage you to differentiate your product strengths through the use of contrasting colors, boxing, or some other means.

3. INSERT

a. General Comments

i. All three strengths are the subject of this ANDA and, therefore, should share the same package insert. Revise your package insert labeling to combine all information for the three strengths (15 mg, 30 mg, and 60 mg).

In addition, we encourage you to include the 100 mg and the 200 mg tablets (subjects of ANDA 74-769), as does the labeling for the reference listed drug, MS CONTIN.

ii. Minor revisions, which are mostly editorial, are indicated on the enclosed mock-up of your draft labeling.

Please revise your container labels and package insert labeling, as instructed above, and submit final printed container labels and draft package insert labeling.

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.

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.

In addition to responding to these deficiencies, please note that the samples of the drug substance, finished product, and all related substances will be requested by an FDA laboratory for methods validation.

The interim dissolution specifications will be set by the Division of Bioequivalence.

Regarding Synthesis:

The DMF (b)(4)(CC) has been reviewed and found deficient. A separate letter outlining the deficiencies has been sent to the DMF holder. These deficiencies must be corrected before your ANDA can be approved.

Regarding method validation

Please respond to following comments for method validation of ANDA #74-769.

(b)(4)(TS)

(b)(4)(TS) [redacted]

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,

/S/ [redacted] 10/5/96

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

ANDA 74-862

A B Generics, L.P.
Attention: James H. Conover
100 Connecticut Avenue
Norwalk, CT 06850-3590

AUG 28 1996

Dear Dr. Conover:

Reference is made to the Abbreviated New Drug Application, and the amendments submitted on May 3 and 8, 1996 for Morphine Sulfate Extended-release Tablets, 15 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The assayed potency and content uniformity results for both the test and reference products should be submitted.

2. We advise submission of the analytical raw data for all subjects in the studies.

3. The representative [redacted] submitted with the study are not legible. Please submit [redacted] with legible labels.

4. Please submit dissolution testing data on the Morphine Sulfate Extended-release Tablets in Simulated Gastric Fluid. The dissolution methodology which is intended for use, along with proposed dissolution specifications (NLT and NMT at each time point) should be submitted.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/ [redacted]

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5.1

ANDA 74-862

MAY 7 1997

AB Generics
Attention: James H. Conover
100 Connecticut Avenue
Norwalk, CT 06850-3690

Dear Dr. Conover:

Reference is made to the Abbreviated New Drug Application, and the amendments submitted on December 10 and 27, 1996, for Morphine Sulfate CR Tablets, 15, 30 and 60 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

The single-dose bioequivalence study #MO93-0903 under fasting and nonfasting conditions (15 mg tablet), the single-dose bioequivalence study #MO94-1103 (30 mg), and the single-dose bioquivalence study #M094-1003 (60 mg) remain incomplete for the following reasons:

1. Submit the criteria for acceptance of batch runs based on standard curves and quality control samples used for each of the above listed studies.

2. Explain the criteria used to select and reassay samples based on sample processing error, [redacted] and pharmacokinetic outlier in the above studies.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/ [redacted]

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

OCT 21 1997

ANDA 74-862

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT: AB Generics L.P. PHONE: ~~203-853-0123~~ 203-854-7286

ATTN: Mary Ann Traut FAX: ~~203-838-1576~~ 203-851-5229

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

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated 74-862, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, and 60 mg.

Reference is also made to your amendment(s) dated February 12, 1997.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (8 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, norwill the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. 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. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

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

OCT 21 [illegible]

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-862 APPLICANT: AB Generics L.P.

DRUG PRODUCT: Morphine Sulfate Extended-Release Tablets, 15 mg, 30 mg and 60 mg.

The deficiencies presented below represent Minor deficiencies.

A. Deficiencies:

1. Please revise your proprietary and established names in your 356h form and resubmit based on Morphine Sulfate Extended-release Tablets.

2. (b)(4)(CC) [redacted]

3. Please incorporate your finished product related substances and degradation limits in your COAs and resubmit.

4. Revised dissolution methods provided in Attachment 26 are not clear. Based on these methods; Dissolution Method-DS2-1HS Rev.1 for 100 and 200 mg tablets: dissolution medium SGF, USP apparatus 1 (basket method), 50 rpm. Sampling time 1,3,9 hrs. Also, Dissolution Method-DS2-1LS Rev.1 for 15, 30 and 60 mg tablets: dissolution medium Water, USP apparatus 1 (basket method), 50 rpm. Sampling time 1,2,6 hrs. Please explain why are you using the different dissolution mediums in your dissolution methods and clarify when you are changing SGF or water to SIF or you have deleted using SIF in your dissolution procedures.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. (b)(4)(CC) [redacted]

2. Please be advised that the suitability of the proposed drug release specifications will be established upon completion of review by the Division of Bioequivalence and should be incorporated into the appropriate chemistry, manufacturing and controls sections of your application. Any changes made to the chemistry, manufacturing and controls sections of your application as a result of responding to the outstanding bioequivalence deficiencies must be submitted for review.

Sincerely yours,

/S/ [redacted]

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