CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74769

CORRESPONDENCE

AB Generics L.P.

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

October 16, 1995

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 20857-2773

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 200 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® 200 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® 200 mg (controlled-release) Tablets is the marketed reference product for this application.

In addition to the archival set of fifteen (15) 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. Thus, this 200 mg ANDA is the first 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, Ph.D.
Executive Director
Drug Regulatory Affairs & Compliance
Telephone: (203) 854-7280

JHC:kh
Enclosure

ANDA 74-769

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

DEC 8 1995

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. We also refer to your correspondence dated November 14, 1995.

NAME OF DRUG: Morphine Sulfate Extended-release Tablets; 200 mg

DATE OF APPLICATION: October 16, 1995

DATE OF RECEIPT: October 19, 1995

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

For you information: In order to qualify a second source of supply for the bulk drug substance the following is required:

1. Manufacturer's Certificate of Analysis

2. Firm's own bulk drug analysis which includes test specifications and data. The specifications of the currently approved product should be examined to determine if physical specifications such as particle size, isomeric forms, etc. are important criteria to be re-evaluated.

3. Executed production batch record for a batch of at least 10% of the regular production run but not less than 100,000 units in the case of oral solid dosage forms, together with finished production specifications and test data, comparative dissolution data if applicable and 3 month accelerated stability data.

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

Should you have questions concerning this application contact:

Timothy Ames
Consumer Safety Officer
(301) 594-0350

Sincerely yours,

/S/ [redacted] 12/7/95

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

ANDA 74-769
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsements: HFD-615/PRickman, /S/ [redacted] 12/4/95 date
HFD-615/SMiddleton [redacted] date
HFD-647/JSimmons [redacted] date
WP File x:\new\firmsam\ABGeneri\ogd74769.f
F/T by hrw 12-04-95
ANDA Acknowledgement Letter!

ANDA 74-769

APR 10 1996

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

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on October 16, 1995, for Morphine Sulfate Extended-release Tablets 200 mg.

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

A. The following comments refer to both the four-way cross-over and multiple-dose bioequivalence studies:

1. It was indicated that the morphine sulfate controlled-release 200 mg tablet, lot #4WD, Purdue Frederick Company, is the test product used in the bioequivalence studies. Please clarify that the test product is AB Generics' product and not Purdue Frederick's product.

2. The following information is required for review:

a. Potency and content uniformity for the test and reference products;

b. The analytical raw data for all subjects in the studies;

c. The criteria for acceptance of batch runs based on standard curves and quality controls samples used for morphine and morphine-6-glucuronide (study #MO94-0309) and for morphine-6-glucuronide (study #MO93-0602); and

d. 3.5" Diskettes in ASCII code for the bioequivalence studies # MO93-0602 and #MO94-030. The diskette should be formatted in ASCII format containing two separate files configured as follows:

1-file: subj seq per trt C_1-C_n auct aucinf cmax tmax kelm Thalf clast tlast

2-file: subj seq per trt (concentrations at sampling times)

where clast is the last measurable concentration and tlast is the time of the last measurable concentration. Fields are delimited by one space and missing values should be indicated by a period (".").

B. The following comments apply to the single-dose, study MO93-0602:

1. The following pharmacokinetic parameters should be submitted for morphine and morphine-6-glucuronide, T1/2, Kel, 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).

2. For morphine-6-glucuronide, the standard curve and controls were aliquoted in 0.5 mL volumes. The unknown samples volumes were aliquoted as following:

Period, Subjects	Time(hr)	Volume(mL)
(b)(4)(CC)		

3. The representative chromatograms of morphine for subject #14 are incomplete. The following missing chromatograms for the following time points and controls should be submitted:

(b)(4)(CC)

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

C. The following comments apply to the Multiple dose study MO94-0309.

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

2. [redacted]

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 Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/ [redacted]

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

AB Generics L.P.

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

November 14, 1995

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 Copies:
Ms. Saundra Middleton,
Bioequivalence Division of Office
of Generic Drugs

Re: Amendment to ANDA No. 74-769
Morphine Sulfate Controlled-Release 200 mg Tablets

Dear Dr. Ganley:

In response to our telephone conversation with Ms. Saundra Middleton, attached hereto please find a replacement page for the above cited ANDA submission which is identified as page 2a **R**.

This replacement page is being submitted to correct the Patent Certification Statement covering Patent Nos. 4,235,870 and 4,366,310 which were noted under a Paragraph IV Certification rather than Paragraph I Certification.

Thank you for your courtesy and cooperation in this matter. If you should have any questions or I can be of further assistance, I can be reached at 203-854-7286.

Sincerely,

Mary Ann Traut

Mary Ann Traut
Associate
Drug Regulatory Affairs & Compliance Department

MAT:kh
Enclosure

RECEIVED
NOV 17 1995
GENERIC DRUGS

g:\sharedpt\dra\mat\msabg\anda\200mg\patent\patcertr.doc

AB Generics L.P.

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

NDA ORIG AMENDMENT

February 16, 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

Main Amendment to 74769 pkt C. Parise

RECEIVED
FEB 22 1996
GENERIC DRUGS

Re: Morphine Sulfate Controlled-Release 100 mg Tablets
74769

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® 100 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® 100 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. Thus, this 100 mg ANDA is the second 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 Conover

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

JHC:kh
Enclosure

ANDA 74-769

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

JUL 31 1996

Dear Dr. Conover:

This is in reference to your abbreviated new drug application dated October 16, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Morphine Sulfate Extended-Release Tablets, 100 mg and 200 mg.

Reference is also made to amendment dated February 16, 1996.

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

/S/ [redacted]
9/18/96

A. Chemistry Deficiencies

CMC
pgs 1-8

B. Labeling Deficiencies

1. GENERAL COMMENT:

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

Morphine Sulfate Extended-release Tablets ___ mg

2. CONTAINER

a. See general comment.

b. Your listing of inactive ingredients on the container labels is not necessary. You may delete this information.

c. Regarding your 100 mg container label: (100s)

i. Increase the readability of the strength. We find the white on light blue difficult to read.

ii. Include the controlled substance symbol on the label. We refer you to 21 CFR 1302.04

for guidance.

3. INSERT

a. General Comments

i. You may use a shared insert for the multiple strengths of this drug product, if you prefer.

ii. Minor revisions, which are mostly editorial, are indicated on the enclosed mock-ups of your draft labeling. In addition, please make the following revisions.

b. DESCRIPTION

i. For the 100 mg tablet

(a). We note that you have not included "magnesium stearate" in the listing of inactive ingredients as seen in your components and composition statements. Please revise and/or comment.

(b) Delete the phrase "and other ingredients". This phrase is reserved for ingredients which are considered to be trade secrets. Refer to USP 23 General Information, Chapter <1091> for guidance.

ii. For the 200 mg tablet

Include the structural formula.

c. CLINICAL PHARMACOLOGY

i. You may delete the first sentence of this section.

ii. The subsection heading Pharmacodynamics should appear with the same prominence as the other subsection headings.

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 collected by an FDA representative 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.

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] 7/30/96

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

Enclosures

3/1

JUN 27 1996

ANDA 74-769

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

Dear Dr. Conover:

Reference is made to the bioequivalence data submitted February 16, 1996, March 11, 1996 and May 8, 1996, for Morphine Sulfate Extended-release Tablets, 100 mg.

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

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

2. Please submit the analytical raw data for all subjects in the studies.

3. 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).

4. Please submit a 3.5" Diskettes in ASCII code for the bioequivalence study #MO94-1002, which contains both morphine and morphine-6-glucuronide data.

5. The representative (b)(4)(CC) submitted by the firm for subjects (#1, #6, #11, #15 and #22) are not legible. The firm is advised to submit (b)(4)(CC) with legible labels.

6. In the study report section, it was specified that twenty-six (26) subjects were enrolled and completed the study. In the analytical report section (page 145), the firm stated that "of the 26 subjects that were enrolled in the study, subject #3 dropped out after Phase I". Please explain this discrepancy.

7. Please submit comparative dissolution data using the following dissolution specifications:

900 mL of water at 37°C using USP 23 apparatus I (basket) at 50 rpm.

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]

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

ANDA 74-769

AB Generics
Attention: James H. Conover
100 Connecticut Avenue
Norwalk CT 06850-3590

MAR - 3 1997

Dear Sir:

Reference is made to the bioequivalence data for Morphine Sulfate Control-Release Tablets, 100 mg, submitted on October 7, 1996.

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

> Though The Division of Bioequivalence has no further questions relating to the single-dose bioequivalence study #M094-1002, conducted by AB Generics L.P., on its Morphine Sulfate Controlled-Release Tablets, 100 mg, lot #4XC, comparing it with MS Contin® Controlled-Release tablets, 100 mg, manufactured by Purdue Frederick Company; the approval of the above strength awaits the results of the review of the response to the deficiencies of the 200 mg strength.

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) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/ [redacted]

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-769

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

JUL 31 1996

Dear Dr. Conover:

This is in reference to your abbreviated new drug application dated October 16, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Morphine Sulfate Extended-Release Tablets, 100 mg and 200 mg.

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

A. Chemistry Deficiencies

CMC
pgs 1-8

B. Labeling Deficiencies

1. GENERAL COMMENT:

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

Morphine Sulfate Extended-release Tablets ___ mg

2. CONTAINER

a. See general comment.

b. Your listing of inactive ingredients on the container labels is not necessary. You may delete this information.

c. Regarding your 100 mg container label: (100s)

i. Increase the readability of the strength. We find the white on light blue difficult to read.

ii. Include the controlled substance symbol on the label. We refer you to 21 CFR 1302.04

for guidance.

3. INSERT

a. General Comments

i. You may use a shared insert for the multiple strengths of this drug product, if you prefer.

ii. Minor revisions, which are mostly editorial, are indicated on the enclosed mock-ups of your draft labeling. In addition, please make the following revisions.

b. DESCRIPTION

i. For the 100 mg tablet

(a). We note that you have not included "magnesium stearate" in the listing of inactive ingredients as seen in your components and composition statements. Please revise and/or comment.

(b) Delete the phrase "and other ingredients". This phrase is reserved for ingredients which are considered to be trade secrets. Refer to USP 23 General Information, Chapter <1091> for guidance.

ii. For the 200 mg tablet

Include the structural formula.

c. CLINICAL PHARMACOLOGY

i. You may delete the first sentence of this section.

ii. The subsection heading Pharmacodynamics should appear with the same prominence as the other subsection headings.

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 collected by an FDA representative for methods validation.

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

Regarding Synthesis:

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]

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

Enclosures

AB Generics L.P.

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

December 3, 1997

SUBMITTED IN DUPLICATE
RESPONSE TO FDA REQUEST FOR INFORMATION
MINOR AMENDMENT
Via Federal Express

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AM

RE: MORPHINE SULFATE EXTENDED-RELEASE TABLETS 100 and 200 mg
ANDA #74-769

Dear Mr. Sporn:

Reference is made to our ANDA submissions for Morphine Sulfate Controlled Release Tablets 15, 30 and 60 mg submitted to the Agency on May 3, 1996. February 23, 1996 and March 11, 1996 respectively. In addition reference is made to our Amendment of February 12, 1997 and the Agency's FAX of October 21, 1997 (Minor Amendment).

For ease of review each of the Agency's minor deficiencies noted in the above FAX will be addressed in the order provided:

CHEMISTRY, MANUFACTURING AND CONTROL DEFICIENCIES

CMC

TRADE SECRET

PAGES 1 – LABELING DEFICIENCIES

extended-release tablets.

LABELING DEFICIENCIES:

CONTAINER:

1. **REQUEST:** We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of your products.

   RESPONSE: In response to the above request, the container labels for Morphine Sulfate Extended-Release Tablets 100 and 200 mg have been revised in order to add a color box around the product strength on each label. The color of the box will be matched to coordinate with the color of each strength tablet. The text for the container labels remains unchanged. [ATTACHMENTS 5].

INSERT

GENERAL:

2.a. **REQUEST:** You may revise "Morphine Sulfate" to read "morphine sulfate" throughout the text of the insert, (note lower case).

RESPONSE: Throughout the text "Morphine Sulfate" has been revised to read "morphine sulfate."

TITLE

2.b. **REQUEST:** Title..... Tablets....(plural)

RESPONSE: The word tablet in the title has been made plural.

DESCRIPTION

2.c.i. **REQUEST:** Include the molecular, 758.85

RESPONSE: The molecular weight 758.85 has been added.

2.c.ii. **REQUEST:** Include the molecular formula; $(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$

RESPONSE: The molecular formula noted above has been included in the attached package inserts.

CLINICAL PHARMACOLOGY

2.d.i. **REQUEST:** Revise the subsection heading, "Pharmacodynamics" so that it has the same prominence as the subsection heading, "Metabolism and Pharmacokinetics".

RESPONSE: The prominence of the subheading has been revised.

2.d.ii. **REQUEST:** Revise "ml" in last line to read "mL"

RESPONSE: ml has been changed to mL.

PRECAUTIONS

2.e.i. **REQUEST:** Pregnancy (Teratogenic Effects - Category C)

Replace the first paragraph with the following text:

Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus.

Morphine sulfate extended-release tablets should be used in pregnant women only when clearly needed. (See also: PRECAUTIONS: Labor and Delivery, and DRUG ABUSE AND DEPENDENCE.).

RESPONSE: The above text has been inserted into each of the attached package insert.

2.e.ii. **REQUEST:** Pediatric Use

Use of morphine sulfate extended-release has not been evaluated systematically in pediatric patients.

RESPONSE: The Pediatric Use statement as been revised as stated above.

DOSAGE AND ADMINISTRATION

2.f.i. **REQUEST:** Conversion from Conventional Oral Morphine to Morphine Sulfate Extended-Release Tablets

The following text should appear as the last 3 sentences in this subsection:

Morphine sulfate extended-release tablets of 15 mg strength should be used for initial conversion for patients whose total daily requirement is expected to be less than 60 mg. Morphine sulfate extended-release tablets of 30 mg strength are recommended for patients with a daily morphine requirement of 60 to 120 mg. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

RESPONSE: The above three sentences have been added to the section entitled: "Conversion from Conventional Oral Morphine to Morphine Sulfate Extended-Release Tablets.

2.f.ii. **REQUEST:** Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets

In patients whose daily morphine requirements are expected to be less than or equal to 120 mg per day, morphine sulfate extended-release tablets of 30 mg strength are recommended for the initial titration period. Once a stable dose regimen is reached, the patient can be converted to the 60 mg or 100 mg morphine sulfate extended-release tablets, or an appropriate combination of tablet strengths, if desired.

RESPONSE: The above two sentences have been added to the section entitled "Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets.

2.f.iii. **REQUEST:** Use of Morphine Sulfate Extended-Release Tablets as the First Opioid Analgesic

Replace the first two sentences with the following text:

There has been no systematic evaluation of morphine as an initial opioid analgesic in the management of pain.

RESPONSE: The sentence above has replaced the first two sentences in this section.

2.f.iv. **REQUEST:** Considerations in the Adjustment of Dosing Regimens

Add the following text as the third paragraph.

For patients with low daily morphine requirements, morphine sulfate extended-release tablets of 15 mg strength should be used.

RESPONSE: The third paragraph of the section noted above have been revised to read as requested.

2.f.v. **REQUEST:** Conversion from Morphine Sulfate Extended-Release Tablets to Parenteral Opioids (Insert for 100 mg strength)

Revise the subsection heading as above and make the following revision in the first sentence (delete reference to 100 mg strength):

...patient from morphine sulfate...

2.f.vi. **REQUEST:** The following comments are specific to the insert submitted for the 200 mg strength and

2.f.vi.A).1. **REQUEST:** Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets.

1. Revise the subsection heading as above (plural "Tablets") and make the following revision in the penultimate sentence of the second paragraph, "...converting a patient to morphine sulfate extended-release tablets directly. The...".

RESPONSE: This section has been revised as requested above.

2.f.vi.A).2. **REQUEST:** 2. Other parenteral...

Make the following revision in the second paragraph, "... daily dose or morphine sulfate extended-release tablets required and rely..."

RESPONSE: The above revision has been incorporated into the attached package insert.

2.f.vi.B) **REQUEST:** Add the subsection, "Use of Morphine Sulfate-Extended-Release Tablets as the first Opioid Analgesic" with the revisions outlined above.

RESPONSE: The above subsection has been added as revised.

2.f.vi.C) **REQUEST:** Special Instructions for Morphine Sulfate Extended-release Tablets 200 mg

Make the following revision in the last sentence, "...**regimen using lower strengths of extended-release morphine sulfate tablets or other opioids.**".

RESPONSE: The last sentence has been revised as requested.

In summary, each labeling deficiency for the INSERT for each tablet strength has been addressed. As noted above, all revisions requested by the Agency have been made. Therefore, attached please find the revised package inserts for Morphine Sulfate Extended-Release Tablets, 15 mg, Morphine Sulfate Extended-Release 30 mg ,Tablets and Morphine Sulfate Extended Release Tablets 60 mg submitted in final print, as requested. [ATTACHMENT 6].

In accordance with 21 CFR 314.94(a) (8) (iv), we have provided side-by-side comparisons of our proposed labeling with the labeling contained in our last submission. All differences have been annotated and explained. [ATTACHMENT 7].

If you have any questions or if I can be of further assistance, please contact me at (203) 854-7286.

Sincerely,
AB Generics L.P.
By

Mary Ann Traut
Associate
Drug Regulatory Affairs & Compliance
The Purdue Frederick Company

/mat
Attachment

AB Generics L.P.

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

NDA ORIG AMENDMENT

December 31, 1996

SUBMITTED IN DUPLICATE
RESPONSE TO FDA REQUEST
MAJOR AMENDMENT - CHEMISTRY

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855

Desk copy: Newark District Office

RE: MORPHINE SULFATE CONTROLLED-RELEASE TABLETS 100 AND 200 MG
ANDA #74-769

Dear Mr. Sporn:

Reference is made to our ANDA submission for Morphine Sulfate Controlled Release Tablets 100 and 200 mg. In addition, reference is also made to the Agency's deficiency letter dated July 31, 1996.

CMC

TRADE SECRET

PAGES 1 - 15

A.9.d.i. REQUEST: Please revise the dosage description section to indicate imprint instead of "indicia".

RESPONSE: Attached are revised stability reports which indicate debossed rather than indicia in the dosage description section.

A.9.d.ii. REQUEST: Please revise and resubmit a tighter hardness limit.

RESPONSE: There are no finished product specifications for hardness. The tablet hardness is controlled during tablet compression. The tablet hardness in-process testing limits have been tightened (b)(4)(CC) for both strengths based on a review of stability data.

A.9.d.iii. REQUEST: Please revise to include related substances test and limits for product in blister packages in your stability testing specifications and resubmit.

RESPONSE: In response to the Agency's letter of December 8, 1995, and on March 14, 1996, AB Generics L.P. formally withdrew the blister packaging format from our ANDA Submission, in the same letter AB Generics L.P. also withdrew (b)(4)(CC) as a second source for the active raw material, morphine sulfate.

A.9.e. REQUEST: Please revise the description, hardness and related substances limits in your stability protocol and reports and resubmit.

RESPONSE: There are no finished product specifications for hardness. The tablet hardness is controlled during tablet compression. The tablet hardness in-process testing limits have been tightened (b)(4)(CC) for both strengths based on a review of stability data.

B.1. REQUEST: Revise the established name on all labels and labeling to read as follows:

MORPHINE SULFATE EXTENDED-RELEASE TABLETS _____ MG

RESPONSE: All labels and labeling have been revised to note the established name of the product as Morphine Sulfate Extended Release Tablets _____mg.

CONTAINER

B.2.a. REQUEST: See General Comment

RESPONSE: Please see response to B.I. above.

B.2.b. REQUEST: Your listing of inactive ingredients on the container labels is not necessary. You may delete this information.

RESPONSE: Attached please find revised container labels wherein the inactive ingredients listing has been deleted. [Attachment 20 - Morphine Sulfate Extended-Release Tablets, 100 mg ; Attachment 21 - Morphine Sulfate Extended-Release Tablets, 200 mg]

B.2.c.i. REQUEST: Increase the readability of the strength. We find the white on light blue difficult to read.

RESPONSE: The readability of the strength has been enhanced by utilizing the color black on white rather than white on light blue for the 100 mg tablet container labels. The 200 mg tablet container labels were also revised to correspond with the 100 mg labels. The 200 mg bottle labels are black on white except for the red triangle which bears the statement "for use in opioid tolerant patients". (See Attachments 20 and 21)

B.2.c.i. REQUEST: Include the controlled substance symbol on the label. We refer you to 21CFR1302.04 for guidance.

RESPONSE: Attached please find revised container labels where the controlled substance symbol is prominently displayed in accordance with 21CFR1302.04. (See Attachments 20 and 21)

INSERT

B.3.a.i. REQUEST: You may use a shared insert for the multiple strengths of this drug product, if you prefer.

RESPONSE: At this time AB Generics, L.P. prefers to keep these inserts separate but reserves the right in the future to utilize a shared insert which has been approved by FDA.

B.3.a.ii. REQUEST: Minor revisions, which are mostly editorial, are indicated on the enclosed mock-ups of your draft labeling. In addition, please make the following revisions.

RESPONSE: Attached please find revised package inserts for both the 100 and 200 mg strengths which has been changed in accordance with the revisions contained in the mock ups enclosed with the Agency's letter. Four copies of each of these draft package inserts are attached.` [Attachment 22 - Morphine Sulfate Extended-Release Tablets, 100 mg; Attachment 23 - Morphine Sulfate Extended-Release Tablets, 200 mg]

B.3.b.i.(a) REQUEST: We note that you have not included "magnesium stearate" in the listing of inactive ingredients as seen in your components and composition statements. Please revise and/or comment.

RESPONSE: Magnesium stearate was inadvertently left off the listing of inactive ingredients for the 100 mg strength tablet, and has been reinstated. (See Attachment 22)

B.3.b.i.(b) REQUEST: Delete the phrase "and other ingredients". This phrase is reserved for ingredients which are considered to be trade secrets. Refer to USP 23 General Information, Chapter <1091> for guidance.

RESPONSE: The phrase "and other ingredients" has been deleted in the attached package inserts. (See Attachments 22 and 23)

B.3.b.ii. REQUEST: Include the structural formula

RESPONSE: The structural formula has been included in the attached revised package inserts. (See Attachments 22 and 23)

B.3.c.i. REQUEST: You may delete the first sentence of this section.

RESPONSE: The first sentence of this section has been deleted. (See Attachments 22 and 23)

B.3.c.ii. REQUEST: The subsection heading Pharmacodynamics should appear with the same prominence as the other subsection headings.

RESPONSE: The subsection heading Pharmacodynamics has been revised to appear with the same prominence as the other subsection headings. (See Attachments 22 and 23)

In accordance with 21 CFR 314.94(a)(8)(iv), attached please find a side-by-side comparison of our previous draft insert (Column 1) with our revised proposed labeling (Column 2). All differences have been annotated and explained. [Attachment 24 - Morphine Sulfate Extended-Release Tablets, 100 mg; Attachment 25 - Morphine Sulfate Extended-Release Tablets, 200 mg]

We verify that the New Jersey District Compliance Office of FDA is being provided with a true and accurate copy of this submission and Form FDA 356h. The New Jersey District Office oversees (b)(4)(CC) drug manufacturing and distribution center site for Morphine Sulfate Controlled Release Tablets, 100 and 200 mg, in the United States market.

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

Sincerely yours,
AB Generics L.P.
By:
James H. Conover, Ph.D.

James H. Conover, Ph.D.
Executive Director
Drug Regulatory Affairs and Compliance
The Purdue Frederick Company
(203) 854-7280

JHC/cby
Attachments

OCT 21 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-769 APPLICANT: AB Generics L.P.

DRUG PRODUCT: Morphine Sulfate Extended-Release Tablets, 100 mg and 200 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. Your response to item 3.b is unacceptable. Individual, total impurities and degradation product limits may not be required by USP 23, but it is your responsibility to have stability indicating method and provide impurity and degradation limits for the raw material.

3. The yield limits for the 100 mg and 200 mg finished products are provided as (b)(4)(CC) Please resubmit tightened limits.

4. Please incorporate your finished product related substances and degradation limits into your blank COAs and resubmit.

5. 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 you are using this different dissolution medium in your dissolutions methods and please clarify when you are changing SGF or water to SIF, or if you have deleted SIF ~~using~~ from your dissolution procedures.

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

1. Please note that (b)(4)(CC) had not responded to the Agency's deficiency letter dated 5-21-96 at the time of this review. Therefore, (b)(4)(CC) still remains deficient.

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 applications. 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

AB Generics L.P.

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

VIA FAX AND FEDERAL EXPRESS

NEW CORRESP BIOAVAILABILITY

October 8, 1997

SUBMITTED IN TRIPLICATE
GENERAL CORRESPONDENCE
RESPONSE TO FDA
REQUEST FOR INFORMATION
DESK COPY: LIZZIE SANCHEZ, CSO

Mr. Douglas Sporn, Director
Food and Drug Administration
CDER/Office of Generic Drugs
Room 296, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA #74-769
Morphine Sulfate Controlled-Release Tablets, 200 mg

Dear Mr. Sporn:

This letter is in response to the telephone conference of October 7, 1997 between yourself and Dr. Makary of the Agency and Dr. James Conover and Ms. Mary Ann Traut on behalf of AB Generics, L.P.

Initially, we would like to reiterate the relationship between AB Generics, L.P. product and the innovator product, MS Contin Tablets, 200 mg in order to assist with the explanation of the use of simulated gastric fluid without enzymes as the dissolution medium for morphine sulfate controlled release tablet, 200 mg.

Although separate legal entities with different ownership, AB Generics L.P. and The Purdue Frederick Company share offices and officers. In addition, the research and development, and the manufacture of the controlled-release products of each company are performed by the same personnel, in the same facilities, using the same equipment. Therefore, in regard to this ANDA submission, we submit that the P.F. Laboratories, Inc. and The Purdue Research Center (Purdue Frederick entities) have served as contract manufacturer and contract laboratory, respectively, for AB Generics L.P., (b)(4)(CC) personnel, facilities and location are identical to the P.F. Laboratories, which is the Purdue Frederick manufacturer (this was explained also in the cover-letter to the original ANDA submission).

By way of background, The Purdue Frederick Company is the holder of approved NDA No. 19-516 for MS Contin Tablets. MS Contin Tablets are the innovator product upon which the ANDA submissions were based for Morphine Sulfate Controlled-Release Tablets as filed by AB Generics L.P. in accordance with the legal relationship explained above. The NDA approved strengths of MS Contin Tablets are 15, 30, 60, 100 and 200 mg Tablets.

RECEIVED

OCT 14 1997

GENERIC DRUGS

MS Contin Tablets 30 mg was the initial NDA Submission; the 15, 60, 100 and 200 mg tablet strengths were all supplements to the 30 mg NDA. The 15, 30, 60 and 100 mg strengths are each slightly different [redacted] morphine increases. However, the 100 mg and 200 mg strengths [redacted]

The approved dissolution medium for the 30 mg MS Contin Tablets was water. When the supplements for 15, 60, 100 and 200 mg tablets were filed, each one used water as the dissolution medium. The 15 and 60 mg MS Contin Tablets were approved by the Pilot Drug Division with water as the dissolution medium. During review of the 100 and 200 mg supplements by the Division of Biopharmaceutics, the reviewer objected to the use of water as the dissolution medium for these higher strength tablets and insisted that simulated gastric fluid without enzymes be used. After much discussion, Purdue Frederick agreed to perform the dissolution of MS Contin 100 and 200 mg Tablets in SGF rather than water and specifications were set. FDA approved Supplement No. 003 to NDA 19-516 (100 mg supplement) with dissolution performed in simulated gastric fluid, on January 6, 1990.

The supplement for the 200 mg strength tablet originally contained dissolution data performed in water. Upon review, FDA again requested that simulated gastric fluid be used as the dissolution medium. As part of our June, 1993 Amendment to this Supplement dissolution was provided in SGF as requested along with comparative dissolution data in water, gastric, intestinal and gastric/intestinal fluids for informational purposes. FDA approved Supplement No. 004 to NDA 19-516, with dissolution performed in simulated gastric fluid, on November 8, 1993.

Initially, the Office of Generic Drugs insisted that AB Generics L.P. file a separate ANDA for each strength tablet; AB Generics complied with this instruction and five separate ANDA submissions were filed. Upon receipt of these submissions, OGD collapsed the five submissions into two ANDAs, ANDA No. 74-862 covering the 15, 30 and 60 mg strengths and ANDA No. 74-769 covering the 100 and 200 mg strengths.

Due to the relationship noted above we were very familiar with the approved dissolution methodology for the innovator drug (MS CONTIN) and therefore AB Generics L.P. produced and tested the Morphine Sulfate Controlled-Release Tablets (all strengths) which were the subject of these ANDA submissions in accordance with those innovator product parameters.

The bioequivalence portion of the 100 mg section of ANDA No. 74-769, with dissolution performed in simulated gastric fluid, was found to be acceptable by letter from the Agency dated March 3, 1997.

We therefore request, based upon the information provided above, that the bioequivalence portion of the 200 mg section of ANDA 74-769 be approved, with the dissolution performed in simulated gastric fluid.

Also, at the request of Dr. Makery, attached please find the dissolution specifications and methodology for each strength of MS Contin Tablets (Purdue Frederick) and Morphine Sulfate Controlled Release Tablets (AB Generics L.P.).

We will be sending the data disk requested via Federal Express on Monday.

These disks will include both the PK parameters and the morphine-6-glucuronide levels for Study No. MO93-0602 and Study No. MO94-0309 as requested.

We look forward to hearing from you in the near future. If I can be of further assistance, please do not hesitate to contact me at the number given below.

Sincerely yours,

A.B. Generics L.P.
By
Mary Ann Traut

Mary Ann Traut, Associate
Drug Regulatory Affairs & Compliance
The Purdue Frederick Company

FEB 10 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-769 APPLICANT: AB Generics L.P.

DRUG PRODUCT: Morphine Sulfate Extended-Release Tablets, 100 mg and 200 mg.

The deficiencies presented below represent Facsimile deficiencies.

Deficiencies:

1. Your individual and total impurities limits for Morphine Sulfate USP are high based upon available data. The data from the (b)(4)(CC) drug substance lots showed that the highest total impurities and maximum individual impurity were (b)(4)(CC) respectively. Please tighten your limits and resubmit.

2. Please incorporate the following dissolution testing and tentative specifications into your stability and finished product testing and resubmit.

   The dissolution testing should be conducted in 900 mL of SGF at 37° C using USP 23 apparatus I (basket) at 50 rpm. The tentative recommended specifications are followings:

   1 hr (b)(4)(CC)
   2 hr
   3hr
   4 hr
   8 hr

Sincerely yours,

/S/

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

FACSIMILE AMENDMENT

FEB 10 1998

ANDA 74-769

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)

854-7286

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

ATTN: Mary Ann Traut FAX: 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 October 16, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended-release Tablets, 100 mg and 200 mg.

Reference is also made to your amendment(s) dated December 3, 1997.

Attached are 2 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

TIM

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-769 APPLICANT: AB Generics, L.P.

DRUG PRODUCT: Morphine Sulfate Controlled Release Tablets, 100 and 200 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of simulated gastric fluid at 37°C, using USP 23 apparatus I (basket) at 50 rpm. Based on the submitted data the following tentative specifications are recommended:

1	hour	(b)(4)(CC)
2	hours	
3	hours	
4	hours	
8	hours	

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

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

labeling current
draft 3/30/98
A. Vega

AB Generics L.P.

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

FACSIMILE AMENDMENT

March 6, 1998

SUBMITTED IN DUPLICATE
RESPONSE TO FDA REQUEST FOR INFORMATION
FACSIMILE DEFICIENCIES
VIA FAX AND FEDERAL EXPRESS

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

Re: Morphine Sulfate Extended-Release Tablets, 100 and 200 mg
ANDA No. 74-769

Dear Mr. Sporn:

This letter is in response to Facsimile deficiencies received on February 10, 1998 for our ANDA Submission on Morphine Sulfate Extended-Release Tablets 100 and 200 mg, ANDA No. 74-769.

1. REQUEST: Your individual and total impurities limits for Morphine Sulfate USP are high based upon available data. The data from the (b)(4)(CC) drug substance lots showed that the highest total impurities and maximum individual impurity were (b)(4)(CC) respectively. Please tighten your limits and resubmit.

RESPONSE: We have considered both the existing data and your request with respect to tightening the limits for individual and total impurities. At this time we submit tentative specifications for Individual Impurities of (b)(4)(CC)

We commit to further re-evaluate these specifications after we gain more experience by sourcing an additional ten (10) lots of active ingredient from (b)(4)(CC)

Attached are revised Certificates of Analysis showing the revised specifications.

RECEIVED
MAR 0 [illegible] 1998
GENERIC DRUGS

2. REQUEST: Please incorporate the following dissolution testing and tentative specifications into your stability and finished product testing and resubmit.

The dissolution testing should be conducted in 900 ml of SGF at 37° C using USP 23 apparatus I (basket) at 50 rpm. The tentative recommended specifications are following:

1 hr	(b)(4)(CC)
2 hr	
3 hr	
4 hr	
8 hr	

RESPONSE: After careful review of the Division's FAX dated February 10, 1998, AB Generics L.P. sent a FAX to the Bioequivalence Reviewer requesting clarification of their proposed dissolution specifications (the five time points as listed above). Information was also provided to the Division regarding the approved dissolution specifications for MS Contin Tablets 100 and 200 mg (Innovator Product) as well as a reiteration of the specifications proposed in our ANDA 74-769. Upon review of the issues raised, the Bioequivalence Division has found the following dissolution specifications (as proposed in ANDA 74-769) to be acceptable:

100 mg Tablets		200 mg Tablets	
Hour 1	(b)(4)(CC)	Hour 1	(b)(4)(CC)
Hour 2		Hour 3	
Hour 9		Hour 9	

In addition, at the request of Mr. Adolph Vezza, the labeling reviewer, we enclose herewith twelve (12) copies each of the container labels and package inserts representing Final Printed Labeling for Morphine Sulfate Extended Release Tablets 100 and 200 mg.

Sincerely yours,

AB Generics L.P.
By

Mary Ann Traut, Associate
Drug Regulatory Affairs & Compliance
Purdue Pharma L.P.
(203) 854-7286

BIOEQUIVALENCY COMMENTS

ANDA: 74-862 and 74-769 APPLICANT: AB Generics

DRUG PRODUCT: Morphine Sulfate CR Tablets, 200 mg, 100 mg, 60 mg, 30 mg and 15 mg

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

Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

For Morphine Sulfate CR Tablets, 200 mg, 100 mg

The dissolution testing should be conducted in 900 mL of simulated gastric fluid, at 37 °C using USP Apparatus 1 (basket) at 50 rpm. The test product should meet the following specifications:

	100 mg Tablets	200 mg Tablets
1 hr	(b)(4)(CC)	(b)(4)(CC)
3 hr		
9 hr		

For Morphine Sulfate CR Tablets, 60 mg, 30 and 15 mg

The dissolution testing should be conducted in 900 mL of water, at 37 °C using USP Apparatus 1 (basket) at 50 rpm. The test product should meet the following specifications:

1 hr	(b)(4)(CC)
2 hr	
6 hr	

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

Sincerely yours,

/S/

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AB GENERICS L.P.
100 Connecticut Avenue
Norwalk, CT 06859-3590

N/FA

FAX COVER SHEET

DATE:	March 11, 1998	**TIME:**	3:51 PM
TO:	Mr. Douglas Sporn Office of Generic Drugs	**PHONE:** **FAX:**	301-827-5849 301-827-4337
FROM:	Mary Ann Traut AB Generics L.P.	**PHONE:** **FAX:**	203-854-7286 203-851-5229
RE:	Morphine Sulfate Extended-Release Tablets100 and 200 mg ANDA #74-769		

Number of pages including cover sheet: 4

Message

Attached please find our response to the telephone request of Dr. Venkaparm of March 11, 1998 relative to AB Generics FAX Amendment of March 6, 1998.

In addition to this Facsimile submission, we are forwarding hard copy of this documentation, in duplicate, Via Federal Express.

Thank you for your attention to this matter. We look forward to hearing from you in the near future. If I can be of assistance please do not hesitate to contact me.

AB Generics L.P.

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

March 11, 1998

SUBMITTED IN DUPLICATE
RESPONSE TO FDA TELEPHONE REQUEST
FACSIMILE AMENDMENT
VIA FAX AND FEDERAL EXPRESS

NEW JERSEY
NC
TO FAX

Mr. Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855

Re: Morphine Sulfate Extended-Release Tablets 100 and 200 mg
ANDA #74-769

Dear Mr. Sporn:

This letter is in response to my telephone conversation of March 11, 1998 with Dr. Venkaparm as well as a chemistry reviewer regarding our Facsimile Amendment dated March 6, 1998.

Regarding Request No. 1, Dr. Venkaparm wished to clarify that the Agency's request was for tightened impurity limits on the drug substance. Although this was clearly understood by A.B. Generics, we inadvertently revised the finished product Certificates of Analysis to show the tightened impurity controls, rather than the Certificate of Analysis for the drug substance, morphine sulfate USP. Therefore, attached please find the following revised documentation:

- Certificate of Analysis for Morphine Sulfate USP (Drug Substance) which shows our current USP testing requirement plus our commitment to perform related substance testing and to apply the new tightened impurity limits to all receipts of morphine sulfate. The tightened Related Substances Limits are as follows: Unknown Impurities NMT (b)(4)(CC)

- Copies of the Finished Drug Product Certificates of Analysis for Morphine Sulfate Extended-Release Tablets 100 and 200 mg are attached just as they were submitted to ANDA 74-769.

- In addition, please delete the word "tentative" from line 3 of our response to Request I as it is my understanding that the revised impurity specifications submitted in the March 6, 1998 Fax Amendment were acceptable to the agency.

Thank you for your assistance in this matter. Please contact me if there are any further questions.

Sincerely yours,

AB Generics L.P.
By
Mary Ann Traut

Mary Ann Traut, Associate
Drug Regulatory Affairs & Compliance
Purdue Pharma L.P.
(203) 854-7286

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE 3/11/98

We called firm to clarify raw material and bioequivalence limits on Morphine Sulfate product. We indicated that tentative specifications are not acceptable. She said that she will talk to Quality Control section and send revised specifications for raw material and also clarify submited drug product specifications.

She informed us that dissolution specifications for 200 mg tablets were set by the Division of Bioequivalence. We told her that we will verify this specifications from the Division of Bioequivalence.

ANDA NUMBER
74-769/74-862

TELECON/MEETING

INITIATED BY
[]APPLICANT/SPONSOR
[x]FDA

MADE
[x]BY TELEPHONE
[]IN PERSON

PRODUCT NAME
Morphine Sulfate

FIRM NAME
AB Generics L.P

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Mary Ann Traut

TELEPHONE NO.
203-845-7286

SIGANTURE S. Rabson

DIVISION II