

# AB Generics L.P.

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

*Labeling revised  
dated 10/1/97  
G.B. 10-10*

**NDA DRUG AMENDMENT**

*N/AL*

February 12, 1997

*DRAFT  
CRJ*

SUBMITTED IN DUPLICATE  
RESPONSE TO FDA REQUEST FOR INFORMATION  
MAJOR AMENDMENT

Field copy to: New Jersey District Office

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 CONTROLLED-RELEASE TABLETS 15, 30 AND 60 MG  
ANDA #74-862

Dear Mr. Sporn:

Reference is made to our ANDA submissions of Morphine Sulfate Controlled Release Tablets, 15, 30 and 60 mg. In addition, reference is also made to the Agency's deficiency letter dated November 8, 1996.

*CMC DELETIONS*

*Pgs 1 - 25*

*TRADE SECRET*

Mr. Douglas Sporn  
Morphine Sulfate Controlled Release Tablets, 15, 30, and 60 mg  
ANDA #74-862  
Major Amendment - CMC

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26

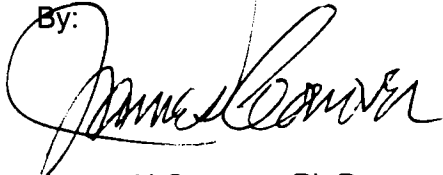
In accordance with 21 CFR 314.94(a)(8)(iv), attached please find a side-by-side comparison of our previous draft insert (Column 1) with our revised proposed labeling (Column 2). All differences have been annotated and explained. [Attachment 27 - Morphine Sulfate Extended Release Tablets, 15 mg; Attachment 28 - Morphine Sulfate Extended Release Tablets, 30 mg; Attachment 29 - Morphine Sulfate Extended Release Tablets, 60 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 Ford FDA 356h. The New Jersey District Office oversees ABG Laboratories, Inc. drug manufacturing and distribution center side for Morphine Sulfate Extended Release Tablets 15, 30 and 60 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.  
Executive Director  
Drug Regulatory Affairs and Compliance  
The Purdue Frederick Company  
(203) 854-7280

12/3/97  
191  
To: [unclear]  
[unclear]  
[unclear]

# AB Generics L.P.

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

Labeling revised  
drafted 1/29/98  
A. V. [unclear]

December 3, 1997

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

**ORIG AMENDMENT**

NIH 11

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 15, 30 AND 60 MG  
ANDA #74-862

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).

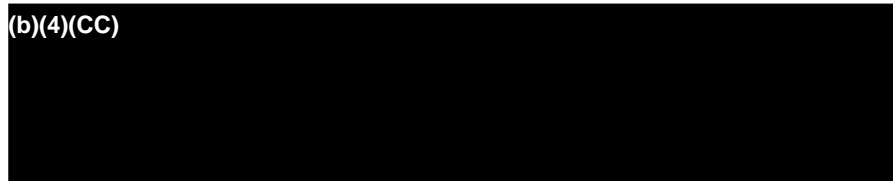
For ease of review each of the Agency's minor deficiencies noted in the above mentioned FAX will be addressed in the order provided:

**CHEMISTRY, MANUFACTURING AND CONTROL DEFICIENCIES**

A.1. **REQUEST:** Please revise your proprietary and established names in your 356h form and resubmit based on morphine sulfate extended-release tablets.

**RESPONSE:** Attached please find a revised form 356h change in the proprietary and established name of the product to morphine sulfate extended-release tablets. [ATTACHMENT 1]

A.2. **REQUEST:** (b)(4)(CC)



DEC 4 1997

RECEIVED

M. [unclear]  
12.5.97

**RESPONSE:** (b)(4)(CC)

A.3. **REQUEST:** Please incorporate your finished product related substances and degradation limits in your COAs and resubmit.

**RESPONSE:** Attached please find templates for Certificates of Analysis for Morphine Sulfate Extended-Release Tablets 15, 30 and 60 mg each of which lists the finished product related substances and degradation limits. [ATTACHMENT 3].

A.4. **REQUEST:** Revised dissolution methods provided in Attachment 26 are not clear. Based on those 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 the different dissolution methods and clarify when you are changing SGF or water to SIF or you have deleted using SIF in your dissolution procedures.

**RESPONSE:** Initially, we would like to reiterate the relationship between the AB Generics, L.P. product and the innovator product, MS Contin Tablets, in order to assist with the explanation of the use of water or simulated gastric fluid without enzymes as the dissolution medium for morphine sulfate extended-release tablets.

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 extended-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) (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 the approved NDA for MS Contin Tablets. MS Contin Tablets are the innovator product upon which the ANDA submissions for Morphine Sulfate Extended-Release Tablets were 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.

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

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 approved dissolution medium for the 30 mg MS Contin Tablets was water. When the supplements for 15, 60 and 100 mg tablets were filed, each one had 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 mg supplement by the Division of Biopharmaceutics, the reviewer objected to the use of water as the dissolution medium for the 100 mg MS Contin Tablet and insisted that simulated gastric fluid without enzymes be used for this higher strength. After much discussion, Purdue Frederick agreed to perform the dissolution of MS Contin 100 mg Tablets in SGF rather than water and specifications were set. MS Contin 200 mg Tablets are compressed into capsule shaped tablets from the same granulate as the MS Contin 100 mg round tablets are compressed. FDA approved Supplement No. 003 to NDA 19-516, 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.

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 extended-release tablets (all strengths) which were the subject of the ANDA submissions in accordance with those parameters.

There is no pH change in the dissolution methodology for MS Contin Tablets or Morphine Sulfate Extended-Release Tablets. A change to SIF from water or SGF has never been a part of the dissolution method for MS Contin Tablets (Purdue Frederick ) or Morphine Sulfate Extended-Release Tablets (AB Generics L.P.) so therefore has never been deleted from these methods.

B.1. **REQUEST:** (b)(4)(CC)

**RESPONSE**

**LABELING DEFICIENCIES:**

**CONTAINER:**

1. **REQUEST:** We acknowledge your comments regarding the differentiation of your product strengths. In particular we recognize your statement that the use of black print on a white background enhances the readability of the labels. We encourage you to prominently differentiate the different strengths to reduce the possibility of medication errors. The differentiation might be accomplished through use of boxing, or other means without compromising your preference for black print on a white background.

**RESPONSE:** In response to the above request, the container labels for Morphine Sulfate Extended-Release Tablets 15, 30 and 60 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. [ATTACHMENT 4].

**INSERT:**

**GENERAL:**

2.a.i. **REQUEST:** We encourage you to 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.

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

2.a.ii. **REQUEST:** Delete the strength from the established name throughout the package inserts.

**RESPONSE:** The strength has been deleted from the established name throughout the attached package inserts.

**DESCRIPTION:**

2.b.i. **REQUEST:** Include the route of administration

**RESPONSE:** The route of administration has been included in the attached package inserts.

2.b.ii **REQUEST:** Revise the molecular weight to read 758.85.

**RESPONSE:** The molecular weight has been revised to 758.85.

2.b.iii. **REQUEST:** Delete the third paragraph (Morphine Sulfate Extended-Release Tablets \_\_\_ mg.)

**RESPONSE:** The third paragraph has been deleted.

2.b.iv. **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.

2.b.v.A). **REQUEST:** First line - Tablet (singular - for 15 and 60 mg inserts)

**RESPONSE:** Tablets in the first line has been made singular

2.b.v.B). **REQUEST:** Revise to read:

. . . U.S.P. In addition each tablet also contains the following inactive . . .

**RESPONSE:** The attached package inserts have been revised as noted above.

### CLINICAL PHARMACOLOGY

#### Pharmacodynamics, Plasma Level- Analgesia Relationships

2.c.i. **REQUEST:** . . . non-tolerant . . . (hyphen - 3 instances),

**RESPONSE:** Hyphens have been added as requested.

2.c.ii. **REQUEST:** . . . 20 ng/mL. (Upper case "L")

**RESPONSE:** 20 ng/ml has been changed to 20 ng/mL.

### INDICATONS AND USAGE

2.d. **REQUEST:** They are intended . . . (rather than "It is intended . . .")

**RESPONSE:** The package inserts have been changed as noted above.

### WARNINGS

2.e. **REQUEST:** Interactions with other CNS depressants, First sentence Morphine Sulfate, like all opioid . . . (for the 30 mg insert only).

**RESPONSE:** The 30 mg package insert has been changed as requested above.



## **PRECAUTIONS**

2.f.i. **REQUEST:** Drug Interactions, last sentence  
... including morphine, may enhance ...

**RESPONSE:** The above change has been made.

2.f.ii. **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 no 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.f.iii. **REQUEST:** Pediatric Use - Revise to read:

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

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

## **OVERDOSAGE**

2.g.i. **REQUEST:** Second paragraph - delete the trailing zero in ... "2 mg" ...

**RESPONSE:** The trailing zero has been deleted.

2.g.ii. **REQUEST:** Indent the fourth paragraph (Note: ...)

**RESPONSE:** Paragraph four has been indented.

## **DOSAGE AND ADMINISTRATION**

2.h.i.A. **REQUEST:** To facilitate the dosing of this drug product we feel that this section should contain mention of the availability of other dosage strengths as well as reference to the dosing information for the other strengths (as does the innovator). See comments below.

2.h.i.B. **REQUEST:** The DOSAGE AND ADMINISTRATION section should be the same for all three proposed inserts to facilitate the dosing of this drug.

**RESPONSE:** The DOSAGE AND ADMINISTRATION sections of these package inserts have been revised to mention the availability of other dosage strengths (as does the innovator). In addition, this section is now the same for all three proposed inserts.

2.h.ii. **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:

The 15 mg extended-release morphine sulfate tablet 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.h.iii. **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 Parental Morphine or Other Options (Parental or Oral) to Morphine Sulfate Extended-Release Tablets.

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

A). Note upper case letters in title for "First Opioid Analgesic".

B). 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 typographical error in A). has been corrected and the statement noted in B). above has replaced the first two sentences in the section noted above.

2.h.v. **REQUEST:** Considerations in the Adjustment of Dosing Regimens

A). Second paragraph - (N.B. extended-release morphine sulfate tablets are a controlled-release formulation which do not . . .

B). The third paragraph should appear as follows:

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

**RESPONSE:** The second and third paragraphs of the section noted above have been revised to read as requested above.

2.h.vi. **REQUEST:** Conversion from Morphine Sulfate Extended-Release Tablets to Parental Options

A). Note the upper case letters in the title (see above).

B). Fourth sentence

Replace the word "morphine" with "morphine sulfate" throughout the sentence (3 instances).

**RESPONSE:** The typographical error noted in A) has been corrected and the word "morphine" has been replaced by "morphine sulfate" as requested in B). above.

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.  
[ATTACHMENTS 5]

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. [ATTACHMENTS 6]

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-862

APPLICANT: AB Generics, L.P.

DRUG PRODUCT: Morphine Sulfate Extended Release Tablets, 15, 30,  
and 60 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 water at 37°C, using USP 23 apparatus I (basket) at 50 rpm. The test product should meet the following tentative specifications:

1 hr	(b)(4)(CC)
2 hrs	
4 hrs	
8 HRS	

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/

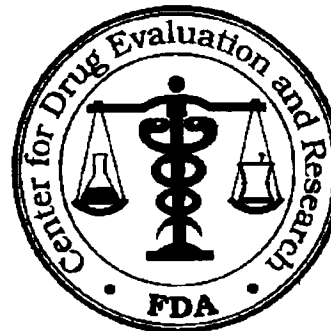
*fw* Dale P. Conner, Pharm. D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**FACSIMILE AMENDMENT**

FEB 9 1998

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 (301-594-0320)



TO: APPLICANT: AB Generics L.P.  
ATTN: Mary Ann Traut

PHONE: 203-853-0123  
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 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 amendment(s) dated December 3, 1997.

Attached are 5 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:**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.** If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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JUN 12 1998

9.1 *from 1, 8*

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 GT	

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

CC: ANDA #74-769 and 74-862  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Secretary - Bio Drug File  
HFD-658 / Reviewer Makary

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Printed in final on 2/25/98

Endorsements: (Final with Dates)  
HFD-658 / Reviewer Makary  
HFD-65 / Team Leader Nerurkar  
HFD-617/ L. Sanchez or N. Chamberlin  
HFD-650 / D. Conner /SI/ [REDACTED] 6/12/98

BIOEQUIVALENCY - ACCEPTABLE

4. STUDY AMENDMENT (STA)

Strengths: 15. 30. 60 mg. 100 and 200 mg  
Outcome: AC

Outcome Decisions:  
AC - Acceptable  
NC - No Action

WINBIO COMMENTS:



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE, HFD-612  
METRO PARK NORTH, ROOM 116  
7500 STANDISH PLACE  
ROCKVILLE, MARYLAND 20855

FACSIMILE TRANSMISSION RECORD

DATE: 6/12/98 FROM: Nancy Chamberlin, Pharm D.  
Project Manager  
TO: Jessie Conover PHONE: (301) 827-5847  
AB Generics FAX: (301) 594-0181  
PHONE: 203-854-7286  
AX: 203-851-5229  
TOTAL NUMBER OF PAGES: 2  
(Including cover sheet)

SPECIAL INSTRUCTIONS:

Correction of 9hour

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# A.B. 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

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

RECEIVED

NC

To File

Re: Morphine Sulfate Extended-Release Tablets 15, 30 and 60 mg  
ANDA #74-862

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.

(b)(4)(TS)

- Copies of the Finished Drug Product Certificates of Analysis for Morphine Sulfate Extended-Release Tablets 15, 30 and 60 mg are attached just as they were submitted to ANDA 74-862.

RECEIVED

MAR 12 1998

GENERIC DRUGS

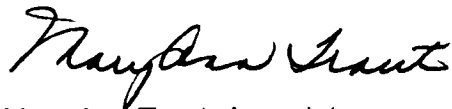
- In addition, please delete the word "tentative" from line 3 of our response to Request I as it is my understanding that the revised impurity specifications submitted in the March 6, 1998 Fax Amendment were acceptable to the agency.

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

Sincerely yours,

AB Generics L.P.

By

A handwritten signature in cursive script, appearing to read "Mary Ann Traut".

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

**CERTIFICATE OF ANALYSIS**

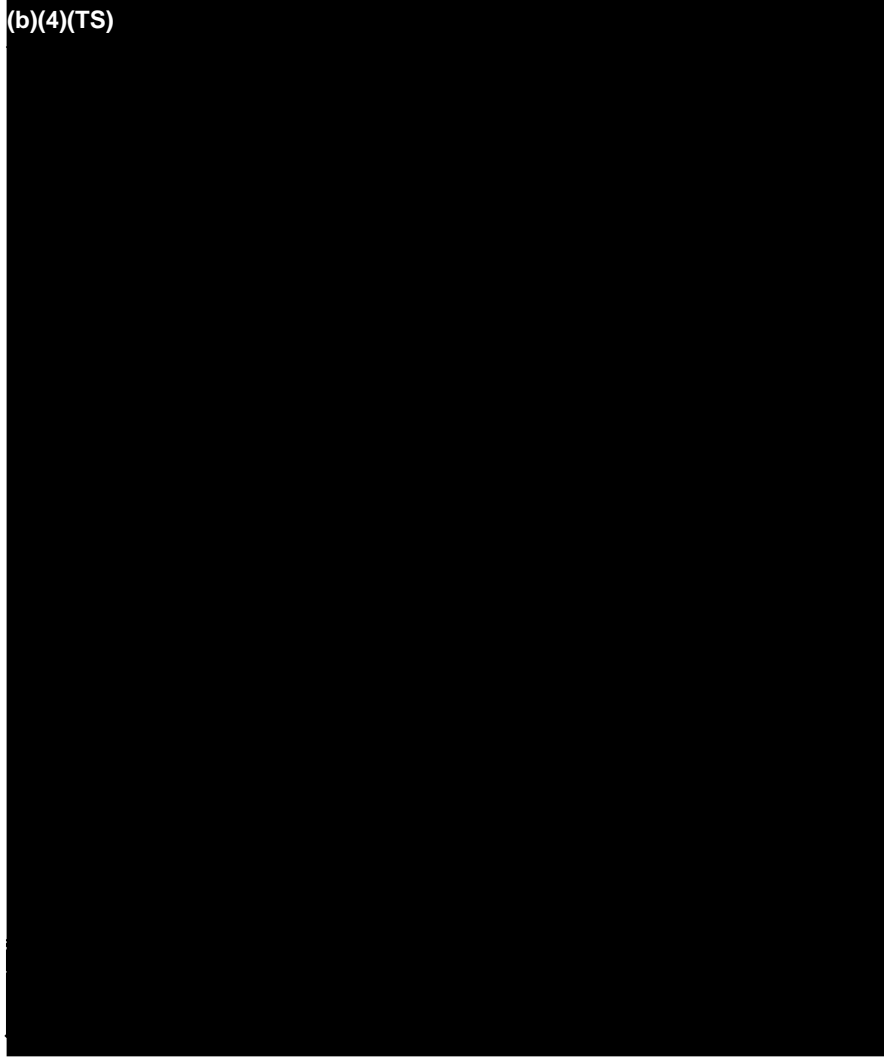
Product: MORPHINE SULFATE , USP  
Lot No.: xxx  
Date Completed: xxxxxxxx

Date:xxxxxx  
Assay Number: xxxxx

<u>Tested For</u>	<u>Specification</u>	<u>Results</u>
-------------------	----------------------	----------------

IDENTIFICATION --

(b)(4)(TS)



\_\_\_\_\_  
R.E. Connor  
Director Quality Control

**CERTIFICATE OF ANALYSIS**

**Product:** MORPHINE SULFATE ER 15 mg Tablets

**Date:**xxxxxx

**Lot No.:** xxxx

**Assay Number:** xxxxx

**Date Completed:** xxxxxxxxx

**Expiration Date:** xxx

<u>Tested For</u>	<u>Specification</u>	<u>Results</u>
<u>Appearance:</u>	Dark blue, round, film coated tablets. Markings consist of "ABG" debossed on one side and "15" debossed on the other. Tablets have no bisect.	
<u>Identification:</u>	(b)(4)(CC)	
<u>Content of Morphine Sulfate 5H<sub>2</sub>O:</u>		
<u>Dissolution</u> 1st Hour 2nd Hour 6th Hour		
<u>Uniformity of Dosage Units:</u>		
<u>Related Substances</u> Unknown Impurities Individual Impurities Total Impurities		

R.E. Connor

\_\_\_\_\_  
Director Quality Control

**CERTIFICATE OF ANALYSIS**

**Product:** MORPHINE SULFATE ER 30 mg Tablets  
**Lot No.:**            xxxx  
**Date Completed:** xxxxxxxxxx

**Date:**xxxxxx  
**Assay Number:**        xxxxx  
Expiration Date. xxx

<u>Tested For</u>	<u>Specification</u>	<u>Results</u>
<u>Appearance:</u>	Light lavender, round, film coated tablets. Markings consist of "ABG" debossed on one side and "30" debossed on the other. Tablets have no bisect.	
<u>Identification:</u>	(b)(4)(CC)	
<u>Content of Morphine Sulfate 5H<sub>2</sub>O:</u>		
<u>Dissolution</u> 1st Hour 2nd Hour 6th Hour		
<u>Uniformity of Dosage Units:</u>		
<u>Related Substances</u> Unknown Impurities Individual Impurities Total Impurities		

R.E. Connor

\_\_\_\_\_  
Director Quality Control

**CERTIFICATE OF ANALYSIS**

**Product:** MORPHINE SULFATE ER 60 mg Tablets

**Date:**xxxxxx

**Lot No.:** xxxx

**Assay Number:** xxxxx

**Date Completed:** xxxxxxxxx

**Expiration Date:** xxx

<u>Tested For</u>	<u>Specification</u>	<u>Results</u>
<u>Appearance:</u>	Light orange, round, film coated tablets. Markings consist of "ABG" debossed on one side and "60" debossed on the other. Tablets have no bisect.	
<u>Identification:</u>	(b)(4)(CC)	
<u>Content of Morphine Sulfate 5H2O:</u>		
<u>Dissolution</u> 1st Hour 2nd Hour 6th Hour		
<u>Uniformity of Dosage Units:</u>		
<u>Related Substances</u> Unknown Impurities Individual Impurities Total Impurities		

R.E. Connor

\_\_\_\_\_  
Director Quality Control

<p align="center"><b>RECORD OF TELEPHONE CONVERSATION/MEETING</b></p>	<p>DATE 3/11/98</p>
<p>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 submitted drug product specifications.</p> <p>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.</p>	<p>ANDA NUMBER 74-769/74-862</p>
	<p align="center">TELECON/MEETING</p>
	<p>INITIATED BY  <input type="checkbox"/> APPLICANT/SPONSOR  <input checked="" type="checkbox"/> FDA</p> <p>MADE  <input checked="" type="checkbox"/> BY TELEPHONE  <input type="checkbox"/> IN PERSON</p>
	<p>PRODUCT NAME Morphine Sulfate</p>
	<p>FIRM NAME AB Generics L.P</p>
<p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Mary Ann Traut</p> <p>TELEPHONE NO. 203-845-7286</p>	
<p>SIGANTURE <i>S. Bayan</i></p>	<p>DIVISION II</p>



*Labels - PI  
Manufacturing Programme  
Labeling Review drafted  
3/17/98 G. Vignola*

*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**

*NO to FAX*

Re: Morphine Sulfate Extended-Release Tablets 15, 30 and 60 mg  
ANDA #74-862

Dear Mr. Sporn:

This letter is in response to Facsimile deficiencies received on February 9, 1998 for our ANDA Submission on Morphine Sulfate Extended-Release Tablets 15, 30 and 60 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)(TS). 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 (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 11 1998

**GENERIC DRUGS**

2. **REQUEST:** Your dissolution sampling time has been changed from 1, 2, 6 hrs to 1, 2, 9 hrs for the 15, 30 and 60 mg tablets in your revised finished product specifications and COAs. Please provide explanation and clarify.

**RESPONSE:** We have not changed nor do we intend to change the sampling times for these three products. This was a simple typographical error. The dissolution sampling times for the 15, 30 and 60 mg Morphine Sulfate Extended-Release Tablets are 1, 2 and 6 hours. We apologize for any confusion that may have occurred.

3. **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 water 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  
4 hr  
8 hr

**RESPONSE:** After careful review of the Division's FAX dated February 9, 1998, AB Generics L.P. sent a FAX to the Bioequivalence Reviewer requesting clarification of their proposed dissolution specifications (the four time points as listed above). Information was also provided to the Division regarding the approved dissolution specifications for MS Contin Tablets 15, 30 and 60 mg (Innovator Product) as well as reiteration of the specifications proposed in our ANDA 74-862. Upon review of the issues raised, we have been informed that the Bioequivalence Division has found the following dissolution specifications (as proposed in ANDA 74-862) to be acceptable.

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

Mr. Douglas Sporn  
Office of Generic Drugs  
FDA

March 6, 1998  
Page 3

In addition, we enclose herewith twelve (12) copies each of the container labels and package inserts representing Final Printed labeling for Morphine Sulfate Extended Release Tablets 15, 30 and 60 mg. Please note that following a telephone conversation with Mr. Adolph Veza, the labeling reviewer, on March 3, 1998, the requested side-by-side comparison of the package inserts will not be submitted as he agreed they would not be required in view of the current submission of Final Printed Labeling.

Sincerely yours,

AB Generics L.P.

By



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