CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74471

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 74-471

DRUG PRODUCT: Nalbuphine Hydrochloride

&M: King Pharmaceuticals, Inc.

DOSAGE FORM: Injection

STRENGTH: 10 mg/mL and 20 mg/mL

CGMP STATMENT: Included - p. 229

EIR STATUS UPDATE: **Pending**

Per the EES on 11/24/97 an acceptable EIR was pending. The evaluations for the other firms were acceptable in September 1996 and may have to be updated as they are over one year old.

BIO STUDY: Satisfactory

A waiver of *in-vivo* study requirements was granted 11/29/94 by Dr. M. Park, HFD-658.

VALIDATION: Satisfactory

Methods validation was performed on the drug substance and drug product by the Southeast Regional laboratory. The SERL found the methods to be satisfactory.

STABILITY: Satisfactory

The stability testing includes:

A two year expiration date is proposed and is supported by the data submitted.

LABELING: Satisfactory for approval - A. Vezza, HFD-613, 11/21/97

STERILIZATION VALIDATION: Satisfactory - Dr. A. High 10/28/97

SIZE OF BIO BATCH: Satisfactory

Four test batches were manufactured in support of this ANDA:

The two original lots manufactured with the drug substance with a content of are:

Lot # PLT-170 (10 mg/mL):
Lot # PLT-169 (20 mg/mL):

Two lots were manufactured with drug substance

Lot # PLT-268 (10 mg/mL):
Lot # PLT-269 (20 mg/mL):

SIZE OF STABILITY BATCHES: Satisfactory

Three month accelerated (40°C) was submitted fot lot #'s PLT-170 and PLT-169 packaged in the proposed market containers, i.e., 10 mL multiple dose vials.

A two year expiration date is proposed which is supported by the data submitted.

PROPOSED PRODUCTION BATCH: Satisfactory

The proposed production batch size for both the 10 mg/mL and 20 mg/ml strengths is Blank batch records were submitted for these proposed production batches.

cc: ANDA 74-471
Division File

12/9/97

CHEMIST: Donald Shostak DATE: October 28, 1997
(Revised 11/24/97)

TEAM LEADER: Ubrani Venkataram DATE: 12/10/97

x:\wpfile\branch7\shostak\74471n04.sum (Disk 16)

FT by: D. Shostak 12/9/97

APPROVAL SUMMARY

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

ANDA Number: 74-471

Date of Submission: December 3, 1997

Applicant's Name: King Pharmaceuticals, Inc.

Established Name: Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL, 10 mL multiple dose vials

CONTAINER (General Comment)

Please submit an additional twelve copies of the final printed container labels individually mounted on heavyweight paper or similar material.

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74471

CORRESPONDENCE

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-423-989-8001
Fax 1-423-989-6113

Thomas K. Rogers, III
Director, Regulatory Affairs

May 29, 1997

VIA FEDERAL EXPRESS

ORIG AMENDMENT
N/AC

Mr. Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
U. S. FOOD & DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: **MAJOR AMENDMENT - ANDA #74-471;**
Nalbuphine Hydrochloride Injection (10 mg/mL & 20 mg/mL)
10 mL Multiple Dose Vials

Dear Mr. Sporn:

An Abbreviated New Drug Application (ANDA) for Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL in 10 mL multiple dose vials was submitted to the Agency by King Pharmaceuticals on February 23, 1994, under Section 505(j) of the Federal Food, Drug and Cosmetic Act. The application was amended on August 8, 1994, February 1, 1996, and December 3, 1996. The most recent "Not Approvable" letter was issued by the Agency on February 14, 1997.

This **Major Amendment**, which includes a **Response to Microbiology Deficiencies**, is intended to respond to all objections cited in the February 14, 1997 letter. To facilitate the review process, each deficiency noted in the letter has been addressed in point-by-point fashion. We are confident that all of the objections have been satisfactorily addressed. In addition to responding to the deficiencies noted, a section titled ***Additional information*** is included at the conclusion of this Amendment. This section describes minor revisions to the proposed Master Batch Records to incorporate

By signature of this letter, it is certified that a complete and true copy of this Major Amendment to the ANDA is being forwarded to the FDA Nashville District Office concurrently with the submission of the application to OGD. Inquiries concerning this application may be directed to my attention at the above listed address. I can be reached by phone directly at 423-989-8172 or via Fax at 423-989-6113.

Yours truly,

KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Senior Director, Regulatory Affairs

cc: Mr. John M. Gregory
Mr. Jefferson J. Gregory
Mr. John A. A. Bellamy
TR/74471-17.doc

MAY 30 1997

GENERIC DRUGS

FEB 14 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 74-471 APPLICANT: King Pharmaceuticals, Inc.

DRUG PRODUCT: Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL.

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

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

Sincerely yours,

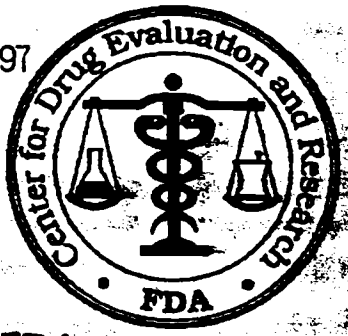
(

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

MAJOR AMENDMENT

ANDA/~~A~~NDA: 74-471

FEB 14 1997



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-277[redacted]

TO: APPLICANT King Pharm. PHONE 1-800-336-7783
ATTN: Tom Rogers FAX 1-423-989-6113

FROM: Tim Ames PROJECT MANAGER (301-594-0309)

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/~~antibiotic~~ application dated 2/23/94, submitted pursuant to Section 505(j)/~~507~~ of the Federal Food, Drug, and Cosmetic Act for Nalbuphine HCl Inj. 10mg/mL and 20mg/mL.

Reference is also made to your amendments dated 12/3/96

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/~~will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS: Note: Due to the change of the

make this a MAJOR amendment.

x:\new\ogdadmin\faxtrak\faxcov.mjr

Microbiology Comments to be Provided to the Applicant

ANDA: 74-471 APPLICANT: King Pharmaceuticals, Inc.

DRUG PRODUCT: Nalbuphine Hydrochloride Injection
10 mg/ml and 20 mg/ml, 10 ml Vials

Microbiology Deficiency:

Please provide a

Please clearly identify your amendment to this facsimile
"RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

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

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-423-989-8001
Fax 1-423-989-6113

December 3, 1996

Thomas K. Rogers, III
Director, Regulatory Affairs

VIA FEDERAL EXPRESS

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: MAJOR AMENDMENT - ANDA #74-471;
Nalbuphine Hydrochloride Injection (10 mg/mL & 20 mg/mL)
10 mL Multiple Dose Vials

Dear Mr. Sporn:

An Abbreviated New Drug Application (ANDA) for Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL in 10 mL multiple dose vials was submitted to the Agency by King Pharmaceuticals on February 23, 1994, under Section 505 (j) of the Federal Food, Drug and Cosmetic Act. The application was amended on August 8, 1994 and February 1, 1996. The most recent "Not Approvable" letter was issued by the Agency on August 30, 1996.

This **Major Amendment** is intended to respond to all objections cited in the August 30, 1996 letter. It is of significance to note that Chemistry Deficiency # 3 requests that the applicant obtain a new

74-471

To facilitate the review process, each deficiency noted in the letter has been addressed in point-by-point fashion. We believe that all of the objections have been satisfactorily addressed. We further believe that adequate information relative to the use of [redacted] in the manufacture of this product is also provided.

By signature of this letter, it is certified that a complete and true copy of this Major Amendment to the ANDA is being forwarded to the FDA Nashville District Office concurrently with the submission of the application to OGD. Inquiries concerning this application may be directed to my attention at the above listed address. I can be reached by phone directly at 423-989-8172 or via Fax at 423-989-6113.

Yours truly,

KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Director, Regulatory Affairs

Enclosure
cc: Mr. John Gregory
Mr. Jefferson Gregory
Mr. John Bellamy

TR/74471-11.doc

ANDA 74-471

King Pharmaceuticals, Inc.
Attention: Thomas K. Rogers, III
501 Fifth Street
Bristol, TN 37620

AUG 30 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated February 23, 1994 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL in 10 mL multiple dose vials.

Reference is also made to your correspondence dated November 11, 1994 and September 14, 1995 and to your amendment dated February 1, 1996.

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

Chemistry Deficiencies:

Labeling Deficiencies:

1. CONTAINER and CARTON

   We find the expression of the product strengths difficult to read, particularly on the carton labeling. Please increase the size and/or prominence of the expressions of strengths.

2. PACKAGE INSERT - Satisfactory

   Please revise your container labels and carton labeling as described above, then prepare and submit final print.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

Reference standards for all tests must be available for collection by FDA staff.

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 MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

8/30/96

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

ANDA 74-471

King Pharmaceuticals, Inc.
Attention: John M. Gregory
501 Fifth Street
Bristol, TN 37620

MAR 1 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated February 23, 1994 , submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nalbuphine Hydrochloride Injection, 10 mg/mL, and 20 mg/mL in 10 mL multiple dose vials.

Reference is also made to your amendment dated August 8, 1994 and correspondence dated April 11, April 29, and August 5, 1994.

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

Chemistry Deficiencies:

In regard to your environmental assessment, we have the following comments:

a. We recommend that you request a categorical exclusion, if applicable, in conformance with 21 CFR 25.24 (c)(1).

b. Please submit a signed statement of compliance with all local, state and federal environmental laws.

Labeling Deficiencies

Container:

1. Revise "DOSAGE" to read "USUAL DOSAGE".

2. Add the following statement in bold print under the statement, "**PROTECT FROM EXCESSIVE LIGHT**":

   Retain in carton until contents are used.

3. We encourage you to differentiate between your product strengths by using contrasting colors and/or boxing.

4. In your composition statement you have indicated that hydrochloric acid and sodium hydroxide are used for pH adjustment. However, only hydrochloric acid is listed in the DESCRIPTION section and on the container label.

5. Insert a space between "10" or "20" and "mg" and/or "mL" (3 locations)

6. Increase the prominence of the strength.

7. ...temperature 15°-30°C (50°-86°F).

Carton:

Please refer to comments under Container and revise as appropriate.

Insert:

1. TITLE

   Revise to read:

   NALBUPHINE HYDROCHLORIDE INJECTION

2. DESCRIPTION

a. Please note that 21 CFR 201.57(a)(1)(iv) states that if a product is sterile, a statement of that fact must be included.

b. Include the molecular formula and the molecular weight.

c. Paragraph 2 -

1) Revise the first sentence read as follows:

Nalbuphine hydrochloride injection is available ... hydrochloride per mL for subcutaneously, intramuscular or intravenous use.

2) The 10 mg/mL strength ...
[When expressing a drug strength please assure that the abbreviation "mg/mL" appears on the same line as the corresponding numerical value.

3) We note, you have indicated that nalbuphine hydrochloride injection is also available in a sulfite and paraben-free formulation. However, we are not aware of your pending ANDA for this formulation. Please comment or delete this last paragraph.

4) Please refer to comment 4 under Container.

3. ACTIONS

a. Revise the section heading to read "CLINICAL PHARMACOLOGY" instead of "ACTIONS". We refer you to 21 CFR 201.56 (d)(1) for further guidance.

b. Last paragraph -

... activity of nalbuphine is one-fourth as potent as ...

4. INDICATIONS

a. Revise the section heading to read, "INDICATIONS AND USAGE" instead of "INDICATIONS". We refer you to 21 CFR 201.56 (d)(1) for further guidance.

b. Sentence 1 -

Nalbuphine hydrochloride injection is ...

c. Sentence 2 -

Nalbuphine hydrochloride injection can ...

5. CONTRAINDICATIONS

Nalbuphine hydrochloride injection should ...

6. WARNINGS

a. Paragraph 1 -

Nalbuphine hydrochloride injection should ...

b. Drug Dependence

Revise to read -

Nalbuphine has been shown to have ...

c. Use in Ambulatory Patients

Revise to read -

Nalbuphine may impair ...

Therefore, nalbuphine hydrochloride injection should be ...

d. Use During Labor and Delivery

Revise as follows:

Nalbuphine can produce ... respiratory depression and cardiac rhythm disturbances in the neonate. It should be used with caution in women during labor and delivery, and newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if nalbuphine has been used.

e. Head Injury and Increased Intracranial Pressure (last sentence):

Therefore, nalbuphine hydrochloride injection should be used in ...

f. Interaction With Other Central Nervous System Depressants (Sentence 1) -

Although nalbuphine possesses narcotic ...

g. Sulfites Sensitivity (Sentence 1) -

Nalbuphine hydrochloride injection contains sodium ...

7. PRECAUTIONS

a. Impaired Respiration

Last two sentences -

...nalbuphine hydrochloride can be reversed by naloxone hydrochloride injection when indicated. Nalbuphine hydrochloride injection should be ...

b. Impaired Renal or Hepatic Function

Revise as follows:

Because nalbuphine is metabolized ...customary doses. Therefore, in these individuals, nalbuphine hydrochloride injection should be ...

c. Cardiovascular System

Revise as follows:

During elevation of nalbuphine hydrochloride injection in ...

8. ADVERSE REACTIONS (Sentence 1) -

The most frequent ... nalbuphine hydrochloride injection is sedation 381 (36%).

9. OVERDOSAGE

a. Add "OVERDOSAGE" as the section heading between the ADVERSE REACTIONS and DOSAGE AND ADMINISTRATIONS sections. We refer you to 21 CFR 201.56 (d)(1) for further guidance.

b. Relocate the subsection, "Management of Overdosage" from the DOSAGE AND ADMINISTRATIONS section to the OVERDOSAGE section.

c. Management of Overdosage

1) Paragraph 1 -

... of naloxone hydrochloride injection is ...
[delete "Narcan" and add "injection"]

2) Paragraph 2 -

... of 72 mg of nalbuphine hydrochloride injection subcutaneously ...

10. DOSAGE AND ADMINISTRATION

a. Paragraph 2 -

The use of nalbuphine hydrochloride injection as a supplement to .... for analgesia. Induction doses of nalbuphine hydrochloride injection range ...as required. The use of nalbuphine hydrochloride injection may be followed ... antagonist naloxone hydrochloride injection.

b. Patients Dependent on Narcotics

1) Sentence 1 -

Patients who have ... administration of nalbuphine hydrochloride injection.

2) Sentence 3 -

...dose of nalbuphine hydrochloride injection can be... temperature or piloerection.

c. Add the following as the last paragraph of this section. We refer you to 21 CFR 201.57 (j) for further guidance.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration , whenever solution and container permit.

11. HOW SUPPLIED

a. Add the following statement at the end of this subsection:

PROTECT FROM EXCESSIVE LIGHT.

Retain in carton until contents are used.

b. Change "multi dose" to "multiple dose".

c. See comment 7 under CONTAINER.

d. Include the date of the latest revisions.

Please revise your container labels, and carton and package insert labeling, then prepare and submit final printed container labels and carton labeling and draft package insert labeling.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

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,

2/28/97

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

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-423-989-8001
Fax 1-423-989-6113

Thomas K. Rogers, III
Director, Regulatory Affairs

February 1, 1996

Charles J. Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: **Major Amendment - ANDA #74-471;**
Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL,
10 mL Multiple Dose Vials

Dear Dr. Ganley:

An Abbreviated New Drug Application (ANDA) for Nalbuphine Hydrochloride Injection was submitted to the Agency by King Pharmaceuticals on February 23, 1994, under Section 505 (j) of the Federal Food, Drug and Cosmetic Act. The application was amended on 8/8/94. A "Not Approvable" letter was subsequently issued by the Agency on March 1, 1995.

This Major Amendment is intended to respond to all objections cited in the March 1, 1995 letter. To facilitate the review process, each deficiency noted in the letter has been addressed in point-by-point fashion. We believe that all of the objections have been satisfactorily addressed within this Amendment. Additionally, requested labeling revisions have been effectuated, and final print labeling for the proposed products is included with this response.

Lastly, by signature of this letter, it is further certified that a complete and true copy of this Major Amendment to the ANDA is being forwarded to the FDA Nashville District Office concurrently with the submission of the application to OGD.

Inquiries concerning this application may be directed to my attention at the above listed address. I can be reached by phone directly at 423-989-8172 or via Fax at 423-989-6113.

Yours truly,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III

CC: Mr. John Gregory
Mr. Jefferson Gregory
Mr. John Bellamy
Mr. Norman Miller

TR/upm

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6282

John Gregory
Chief Executive Officer

August 5, 1994

FE 505(b)(2)(A) 8-25-94 Chris 8/26/94

NEW CORRESP NC

Mr. Doug Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Amendment - ANDA #74-471;
Nalbuphine Hydrochloride Injection, 10mg/mL and 20mg/mL
10mL Multiple Dose Vials

NEW

Dear Mr. Sporn:

An Abbreviated New Drug Application (ANDA) for Nalbuphine Hydrochloride Injection was submitted to the Agency on February 23, 1994, under Section 505(j) of the Federal Food, Drug and Cosmetic Act. Notification of refusal to file the ANDA under 21 CFR 314.101(d)(3) was received in a letter dated March 24, 1994. In response to the Agency's letter, an informal conference was requested for the purpose of clarifying some of the points raised. A conference was granted and was held on June 16, 1994. We feel that we can now satisfactorily address the deficiencies of the submission.

This Amendment is intended to respond to all objections cited in the March 24, 1994 letter. To facilitate the review process, each deficiency noted in the letter has been addressed in point-by-point fashion. Information relative to two new exhibit batches intended to satisfy scale-up requirements has been included in this Amendment. Additionally, updated stability data for the batches included in the February 23, 1994, submission are provided.

Inquiries concerning this application may be directed to my attention at the above listed address or by calling (615) 989-6200.

Yours truly,

KING PHARMACEUTICALS, INC.

John M. Gregory
Chief Executive Officer

ORIGINAL

Attachment - Field Copy Certification

RECEIVED
AUG 10 1994
GENERIC DRUGS

8/16/94

ANDA 74-471

King Pharmaceuticals, Inc.
Attention: John M. Gregory
501 Fifth Street
Bristol, Tennessee 37620

SEP 2 1994

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated March 24, 1994, and your amendment dated August 8, 1994.

NAME OF DRUG: Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL, 10 mL multiple dose vials.

DATE OF APPLICATION: February 23, 1994

DATE OF RECEIPT: February 24, 1994

DATE ACCEPTABLE FOR FILING: August 9, 1994

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

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

Should you have questions concerning this application, contact:

Tim Ames
Consumer Safety Officer
(301) 594-0305

Sincerely yours,

Robert W. Pollock for 9-2-94
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA74-471
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/GJohnston, Chief_____date
HFD-615/PRickman, CSO_____date 9/2/94
HFD-615/KRoberts, CSO_____date
HFD-647/JSimmons, Supervisory Chemist_____date
HFD-613/JPhillips, Chief_____date
WP File B:\ackanda\74471.ack
F/T hrw 9-2-94/ANDA Acknowledgement Letter!

ORIGINAL

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6232

NDA ORIG AMENDMENT

August 8, 1994

Mr. Doug Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Amendment - ANDA #74-471;
Nalbuphine Hydrochloride Injection, 10mg/mL and 20mg/mL,
10mL Multiple Dose Vials

Dear Mr. Sporn:

An Abbreviated New Drug Application (ANDA) for Nalbuphine Hydrochloride Injection was submitted to the Agency on February 23, 1994, under Section 505(j) of the Federal Food, Drug and Cosmetic Act. Notification of refusal to file the ANDA under 21 CFR 314.101(d)(3) was received in a letter dated March 24, 1994. In response to the Agency's letter, an informal conference was requested for the purpose of clarifying some of the points raised. A conference was granted and was held on June 16, 1994. We feel that we can now satisfactorily address the deficiencies of the submission.

This Amendment is intended to respond to all objections cited in the March 24, 1994 letter. To facilitate the review process, each deficiency noted in the letter has been addressed in point-by-point fashion. Information relative to two new exhibit batches intended to satisfy scale-up requirements has been included in this Amendment. Additionally, updated stability data for the batches included in the February 23, 1994 submission are provided.

Inquiries concerning this application may be directed to my attention at the above listed address or by calling (615) 989-6200.

Yours truly,

KING PHARMACEUTICALS, INC.

John M. Gregory
Chief Executive Officer

Attachment - Field Copy Certification

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6232

August 8, 1994

Mr. Doug Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Amendment - ANDA #74-471;
Nalbuphine Hydrochloride Injection, 10mg/mL and 20mg/mL,
10mL Multiple Dose Vials

Dear Dr. Williams:

In accordance with 21 CFR 314.60, the purpose of this letter is to certify that a true copy of the above referenced Amendment, submitted to the Office of Generic Drugs, on August 8, 1994 was sent on the same date to the Nashville District of the Food and Drug Administration.

Yours sincerely,

KING PHARMACEUTICALS, INC.

Norman T. Miller
Director, Regulatory Affairs

Attachment
(Federal Express
Tracking # 0791854711)

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

Thomas K. Rogers, III
Manager
Regulatory Affairs

NAI "Will Respond" 10/4/95

September 14, 1995

Mr. Douglas L. Sporn, Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: ANDA 74-471, Nalbuphine HCl Injection, 10 mg/mL & 20 mg/mL (10 mL Vials)

Dear Mr. Sporn:

This letter is to acknowledge receipt of the Not Approvable Letter issued from your office on March 1, 1995, relative to the above referenced abbreviated new drug application. The application was originally submitted on February 23, 1994, and amended on August 8, 1994.

Pursuant to 21 CFR 314.120, notice is hereby given that, though we are not prepared to respond within the 180 day limit, we fully intend to amend the application such that the deficiencies stated in the March 1, 1995, letter will be satisfactorily addressed and resolved. It is anticipated that an amendment to the application will be on file with the Agency within the next 60 - 90 days. Accordingly, we request that the review period for this application be extended in anticipation of the forthcoming amendment.

Yours truly,

Thomas K. Rogers, III
Director, Regulatory Affairs

cc: Jeff Gregory
John Gregory
Norm Miller

/TR: 74471-01.doc

RECEIVED
SEP 21 1995
GENERIC DRUGS

Received 9-26-95

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6113

Thomas K. Rogers, III
Manager
Regulatory Affairs

November 11, 1994

Food and Drug Administration
ATTN.: Dr. Don Shostak
OGD MPN-2 HFD-647
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

RE: ANDA 74-471 Nalbuphine Hydrochloride Injection

Dear Dr. Shostak:

Three copies of the test methods relative to the application referenced above which you requested by telephone on November 10, 1994, are included for your review. Test methods for Nalbuphine HCl drug substance and drug product release test methods as well as referenced laboratory procedures for sterility tests and bacterial endotoxin tests are provided.

We appreciate the opportunity to respond to your needs during the review process. If we can be of any further assistance, please do not hesitate to contact either Norman Miller, Director of Regulatory Affairs, or myself. (Telephone: Norman Miller, 615-989-6253; Thomas Rogers, 615-989-6237)

Yours truly,

Thomas K. Rogers, III

cc: Norman Miller
Central File

RECEIVED
NOV 14 1994
GENERIC DRUGS

NAL

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-615-989-6200
Fax 1-615-989-6232

NAZ Noted meeting requested by K Roberts

April 29, 1994

ORIGINAL

Robert W. Pollock, Director
Division of Labeling and Program Support HFD-632
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

RECEIVED
NOV 04
GENERIC DRUGS

Re: Informal Conference Request
1) ANDA 74-471, Nalbuphine Hydrochloride Injection

Dear Mr. Pollock:

As was suggested in a telephone conversation on April 18, 1994, with Ms. Roberts from your office, we are submitting a revised request for an informal conference which includes an agenda and proposed meeting date which were omitted from our original request of April 11, 1994.

There are two major topics we would like to discuss in this meeting, which include the following:

ANDA 74-471, NALBUPHINE HYDROCHLORIDE INJECTION, 10mg/mL and 20mg/mL IN MULTIDOSE VIALS

Your letter of March 24, 1994, informing us of your refusal to file, lists four (4) items on page one. We would like to discuss the last item on that page which addresses the scale-up requirements. The FDA Policy and Procedure Guide 22-90 and the FDA letter of August 4, 1993, have been reviewed, and we believe the batch scale-up outlined in the submission meets the guideline criteria.

Our Exhibit batch of Nalbuphine was packaged into vials, when combined equals Our interpretation of the guidelines is that we would be allowed to scale-up batch size. As indicated in our submission, however, we wish to scale-up batch to only a batch size. We would like to obtain clarification on this point.

P'

RECEIVED
MAY 04 1994
GENERIC DRUGS

PROPOSED MEETING DATE

If your schedule permits, we would like to meet with you at your headquarters on Tuesday, May 24, 1994. If this is not suitable, please notify us of your availability so a new date can be set.

If you should have any questions or need clarification on any points, please contact me directly at (615) 989-6253.

LIST OF ATTENDEES

We anticipate having the following individuals in attendance at the meeting:

Jeff Gregory, V.P. and General Manager
John McCoy, V.P., Quality Management
Willard Lester, Treasurer and V.P. of Legal Affairs
Norman T. Miller, Director, Regulatory Affairs
Tom Rogers, Manager, Scientific Development

It is also a possibility that a representative will be in attendance, although this has not been confirmed at this time.

Sincerely,

King Pharmaceuticals, Inc.

Norman T. Miller

Norman T. Miller
Director, Regulatory Affairs

NTM:ms

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

KING PHARMACEUTICALS

1-800-336-7783
1-615-989-6200
Fax 1-615-989-4232

VAI
Sat Review
K Weiler
4-18-94

April 11, 1994

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855-2773

RE: ANDA 74-471; Nalbuphine Hydrochloride Injection, 10mg/mL and 20mg/mL, 10mL Multi Dose Vial

At this time, we would like to request an informal conference to discuss the above referenced ANDA. In attendance will be Norman Miller, Willard Lester and myself.

Please notify me at the above address or at (615) 989-6200 with a date and time which is convenient for you.

Your assistance in this matter is greatly appreciated.

Sincerely,

KING PHARMACEUTICALS, INC.

Jefferson J. Gregory
Vice President-General Manager

ORIGINAL

RECEIVED
APR 12 1994
GENERIC DRUGS

ANDA 74-471

MAR 24 1994

King Pharmaceuticals, Inc.
Attention: John Gregory
501 Fifth Street
Bristol, TN 37620

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated February 23, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL, 10 mL multiple dose vials.

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

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

You have failed to provide a certification that a true third (field) copy of the technical sections of the application has been submitted to the FDA district office. Refer to sections 21 CFR 314.94(d)(5) and 314.440 of the Final Rule, published in the Federal Register, September 9, 1993, pages 47351 and 47352.

You have failed to provide a completed FDA Form 356(h) with an original signature.

Although inactive ingredients for parenteral drug products may differ from the reference listed drug in substance to adjust pH, you have failed to provide information demonstrating that these differences do not affect the safety of the proposed drug product as required in 21 CFR 314.94(a)(9)(iii).

The master production batch records submitted for your proposed products do not comply with scale-up requirements set forth in Policy and Procedure Guide 22-90. We refer you to the August 4, 1993, letter to industry (see attached copy) for further guidance regarding scale-up of parenteral products. Please provide revised master product batch records reflecting no more than a ten-fold scale-up from the exhibit batches.

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

In addition, please note you have failed to provide certifications with original signatures as required by the Generic Drug Enforcement Act (GDEA) of 1992 [GDEA Sections 306(k)(1) and (2)]. Please provide revised certifications.

Please also identify the function performed at each outside testing laboratory listed in your application.

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

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

Khyati Roberts
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

3/24/94

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: August 4, 1993 industry letter

ANDA#74-471
cc: DUP/Jacket
Division File
HFD-82
Field copy
HFD-600/Reading File
HFD-615/MBennett

Top copy Revised 3/23/94

Endorsements: HFD-615/GJohnston, Chief ____ date 3/23/94
HFD-615/PRickman, CSO ____ date 3/18/94
HFD-615/KRoberts, CS ____ date 3/17/94
HFD-647/JSimmons, Chem Branch ____ date 3.20.94
WP File B:\Roberts\74471.ref
F/T File hrw 3-17-94
ANDA Refuse to File!

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

KING PHARMACEUTICALS

1-800-336-7783
1-615-989-6200
Fax 1-615-989-4232

please to file 505(b)(2)(A) release 3.4.94 3/9/94

February 23, 1994

Roger Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Abbreviated New Drug Application for Nalbuphine Hydrochloride Injection (Nalbuphine Hydrochloride) 10mg/mL - 10mL Multi Dose Vial and 20mg/mL - 10mL Multi Dose Vial

Dear Dr. Williams:

King Pharmaceuticals, Inc., 501 Fifth Street, Bristol, Tennessee 37620, is submitting herewith an Abbreviated New Drug Application for the above referenced prescription drug product. This application, which consists of archival and review copies of six (6) volumes each, as well as three (3) separate copies of the Methods Validation Data, is submitted in accordance with 21 U.S.C. §355(j) and the corresponding regulations of 21 CFR 314; and is based on the approved drug, Nubain 10mg/mL and 20mg/mL [DuPont], listed in the 1993 Approved Drug Products With Therapeutic Equivalence Evaluations [the "Orange Book"], 13th Edition, page 3-200.

From the pilot batch records contained within this submission, it is readily apparent that batches of the two product concentrations were subdivided for the purpose of filling product into both 10mL and 20mL vials. This action was taken after consultation with the Office of Generic Drugs. (See copy of memorandum appended as Attachment 1.) Stability data have been generated from both vial sizes. It is out intention to file a Suitability Petition for the 20mL vial size at a later date. This petition will then subsequently be followed by a supplemental filing to this application pertaining to the larger vial size.

We also wish to bring to your attention the fact that the proposed manufacturing

To alleviate the potential for any confusion, we would also point out that many documents contained within this submission bear the heading of RSR Laboratories, Inc. while other documents are on King Pharmaceuticals, Inc. letterhead. All assets of RSR Laboratories associated with the manufacture of pharmaceuticals were recently acquired by King Pharmaceuticals, so documents generated prior to that acquisition reflect the previous ownership of the company. Notification of this transfer of ownership has been recently forwarded to your attention in separate correspondence.

Inquiries concerning this application may be directed to my attention at the above listed address or by calling (615) 989-6283.

We respectfully request your timely review of this submission.

Yours sincerely,

John Gregory
Chief Executive Officer

xc: Nashville District (1 copy)
FDA (2 copies; 1 Review, 1 Archival)
File (1 copy)