CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

89-557

Generic Name:	Hydrocodone bitartrate and Acetaminophen Elixir 5mg/500mg per 15mL
Sponsor:	Mikart, Inc.
Approval Date:	April 29, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557

APPROVAL LETTER

ANDA 89-557

APR 29

Mikart, Inc.
Attention: Ms. Cerie B. McDonald
2090 Marietta Blvd., N.W.
Atlanta, GA 30318

Dear Ms. McDonald:

Please refer to your abbreviated new drug application dated September 15, 1986, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir, 5 mg/500 mg per 15 mL.

Reference is also made to your communications dated October 9, 1991, and January 14, January 22, January 27, March 9, and April 24, 1992.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your 5 mg/500 mg per 15 mL Elixir will have the same therapeutic effect the listed drug (Vicodin Tablets manufactured by Knoll Pharmaceutical Company).

Any significant change in the conditions outlined in this abbreviated application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.70 of the Regulations.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80 and 314.81 of the Regulations.

This administration should be advised of any change in the marketing status of this drug.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

For Subsequent Campaigns: We call your attention to Section 314.81(b)(3) of the Regulations which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

4/29/92

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 89-557
DUP/Division File
HFD-82 (if w/d, AP, or R/F letter)
HFC-130 JAllen
HFD-638/KShah K Shah 4-29-92
HFD-637/FFang/LTang/4-22-92 4/28/92
HFD-637/JMastronardy/date drafted JM 4/28/92
R/D initialed by FFang
LCT/4-22-92/89557N03.LLT
F/T by typist/date 4/28/92
Approval
Disk Approval #2

4/29/92 FEA pending
4/29/92 T.Wu 4/29/92

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557

FINAL PRINTED LABELING

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR
5 mg/500 mg per 15 mL

C III

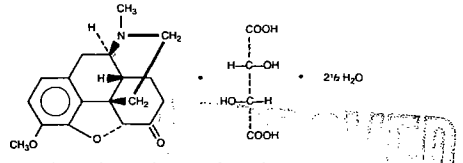
DESCRIPTION:

Hydrocodone* Bitartrate and Acetaminophen Elixir contains:

	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
(*WARNING: May be habit forming)		
Acetaminophen	167 mg	500 mg
Alcohol	7%	7%

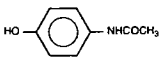
Also contains citric acid anhydrous, ethyl maltol, glycerin, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol solution, sucrose, with D&C Yellow #10 and FD&C Blue #1 as coloring and natural and artificial flavoring.

Hydrocodone bitartrate is an opioid analgesic and antitussive which occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is: 4,5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). Its structure is as follows:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\,1/2\,H_2O$ M.W. 494.50

Acetaminophen, 4'-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder possessing a slightly bitter taste. Its structure is as follows:



$C_8H_9NO_2$ M.W. 151.16

CLINICAL PHARMACOLOGY:

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

Radioimmunoassay techniques have recently been developed for the analysis of hydrocodone in human plasma. After a 10 mg oral dose of hydrocodone bitartrate, a mean peak serum drug level of 23.6 ng/mL and an elimination half-life of 3.8 hours were found.

The analgesic action of acetaminophen involves peripheral and central influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing. Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract, producing maximum serum concentrations within 30 minutes to one hour. The plasma half-life in adults and children ranges from 0.90 hours to 3.25 hours with an average of approximately 2 hours. The drug distributes uniformly in most body fluids and is approximately 25% protein bound. Acetaminophen is conjugated in the liver, with less than 3% of the dose excreted unchanged in 24 hours. The primary metabolic pathway is conjugation to sulfate and glucuronide by-products. A minor oxidative pathway forms cysteine and mercapturic acid. These compounds are subsequently excreted by the kidneys into the urine.

INDICATIONS AND USAGE:

For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS:

Hypersensitivity to acetaminophen or hydrocodone.

WARNINGS:

Respiratory Depression:

At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure:

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions:

The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS:

Special Risk Patients:

As with any narcotic analgesic agent, Hydrocodone Bitartrate and Acetaminophen Elixir should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Information for Patients:

Hydrocodone Bitartrate and Acetaminophen Elixir, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Cough Reflex:

Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Hydrocodone Bitartrate and Acetaminophen Elixir is used postoperatively and in patients with pulmonary disease.

Drug Interactions:

Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Hydrocodone Bitartrate and Acetaminophen Elixir may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus.

Usage in Pregnancy:

Teratogenic Effects: Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. Hydrocodone Bitartrate and Acetaminophen Elixir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Chlorpromazine 0.7 to 1 mg/kg q6h, and paregoric 2 to 4 drops/kg q4h, have been used to treat withdrawal symptoms in infants. The duration of therapy is 4 to 28 days, with the dosage decreased as tolerated.

Labor and Delivery:

As with all narcotics, administration of Hydrocodone Bitartrate and Acetaminophen Elixir to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Hydrocodone Bitartrate and Acetaminophen Elixir, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System:

Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System:

The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of Hydrocodone Bitartrate and Acetaminophen Elixir may produce constipation.

Genitourinary System:

Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported.

Respiratory Depression:

Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated.

DRUG ABUSE AND DEPENDENCE:

Hydrocodone Bitartrate and Acetaminophen Elixir is subject to the Federal Controlled Substances Act (Schedule III).

Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, Hydrocodone Bitartrate and Acetaminophen Elixir should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Hydrocodone Bitartrate and Acetaminophen Elixir is used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE:

Acetaminophen:

Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

Hydrocodone:

Signs and Symptoms: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) should be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION:

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one or two tablespoonfuls every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablespoonfuls.

HOW SUPPLIED:

Hydrocodone* Bitartrate and Acetaminophen Elixir is a green, tropical fruit punch flavored liquid containing 5 mg hydrocodone* bitartrate (*WARNING: May be habit forming), and 500 mg acetaminophen per 15 mL, with 7% alcohol. It is supplied in containers of 4 fl oz (118 mL), NDC 50474-908-04 and in containers of 16 fl oz (473 mL), NDC 50474-908-16.

Storage: Store at controlled room temperature 15–30°C (59–86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

A Schedule III Narcotic.

Manufactured for:
RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35216

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 2/91

Code 539A00

NDC 50474-908-16 C III

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR

5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7 %	7 %

(*WARNING: May be habit forming)

CAUTION: Federal law prohibits dispensing without prescription.

CONTENTS: 1 Pint (473 mL)

USUAL DOSAGE: The usual adult dosage is one or two tablespoonfuls every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablespoonfuls.

See package insert for full information.

Manufactured for:
RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35236

Code 539A16

Rev. 02/90

Lot No.:
Exp. Date:

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature 15–30°C (59–86°F).

WARNING: Keep this and all medications out of the reach of children.

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

APPROVED

APR 29

MAR 9 1992

0010

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature 15–30°C (59–86°F).

WARNING: Keep this and all medications out of the reach of children.

APPROVED

Lot No.:

Exp. Date:

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

NDC 50474-908-04

(C) III

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR

5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7%	7%

(*WARNING: May be habit forming)

CAUTION: Federal law prohibits dispensing without prescription.

CONTENTS: 4 fl oz (118 mL)

USUAL DOSAGE: The usual adult dosage is one or two tablespoonfuls every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablespoonfuls.

See package insert for full information.

APR 29 1992

Manufactured for:
RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35216

Rev. 02/90 Code 539A04

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature 15–30°C (59–86°F).

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Lot No.:

Exp. Date:

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

NDC 50474-908-04

(C) III

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RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35216

Rev. 02/90 Code 539A04

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Lot No.:

Exp. Date:

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

NDC 50474-908-04

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See package insert for full information.

Manufactured for:
RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35216

Rev. 02/90 Code 539A04

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.

STORAGE: Store at controlled room temperature 15–30°C (59–86°F).

WARNING: Keep this and all medications out of the reach of children.

Lot No.:

Exp. Date:

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

NDC 50474-908-04

(C) III

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR

5 mg/500 mg per 15 mL

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See package insert for full information.

MAR 9 1992

Manufactured for:
RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35216

Rev. 02/90 Code 539A04

89557 ORIG N/AC FPL

PROFESSIONAL SAMPLE

Store at controlled room temperature 15–30°C (59–86°F).

WARNING: Keep this and all medications out of the reach of children.

Lot No.:

Exp. Date:

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

NDC 50474-908-01

HYDROCODONE* BITARTRATE AND ACETAMINOPHEN ELIXIR

5 mg/500 mg per 15 mL

Contains:	Per 5 mL	Per 15 mL
Hydrocodone* Bitartrate	1.67 mg	5 mg
(*WARNING: May be habit forming)		
Acetaminophen	167 mg	500 mg
Alcohol	7 %	7 %

CAUTION: Federal law prohibits dispensing without prescription.

CONTENTS: 1 fl oz (30 mL)

USUAL DOSAGE: The usual adult dosage is one or two tablespoonfuls every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablespoonfuls.

See package insert for full information.

APPROVED APR 29 1992

Manufactured for:
RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35216

Rev. 02/92 Code 539A01

PROFESSIONAL SAMPLE

Store at controlled room temperature 15–30°C (59–86°F).

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Lot No.:

Exp. Date:

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

NDC 50474-908-01

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5 mg/500 mg per 15 mL

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APPROVED APR 29 1992

Manufactured for:
RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35216

Rev. 02/92 Code 539A01

PROFESSIONAL SAMPLE

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Lot No.:

Exp. Date:

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MIKART, INC.
Atlanta, GA 30318

NDC 50474-908-01

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Birmingham, AL 35216

Rev. 02/92 Code 539A01

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MIKART, INC.
Atlanta, GA 30318

NDC 50474-908-01

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See package insert for full information.

Manufactured for:
RUSS PHARMACEUTICALS, INC.
Birmingham, AL 35216

Rev. 02/92 Code 539A01

MAR 9 1992

0004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557

CSO LABELING REVIEW(S)

~~MAR 2 7 1992~~

MAR 3 0 1992

REVIEW OF PROFESSIONAL LABELING

Original Amendment

FPL - Container Labels and Package Insert Labeling

DATE OF REVIEW: March 23, 1992

AADA #: 89-557

NAME OF FIRM: Mikart, Inc.

NAME OF DRUG: Generic: Hydrocodone Bitartrate and Acetaminophen Elixer, 5 mg/500 mg per 15 mL

DATE OF SUBMISSION: March 9, 1992

COMMENTS:

Container: Satisfactory in FPL for 1 fl oz (professional sample) 4 fl oz, pint and

Insert: Satisfactory in FPL

RECOMMENDATIONS:

For the Record:

A. This review is based on the labeling guidance revised August, 1987 with minor modification.

B. The use of the name "Lortab" is still unresolved, Mikart proposes not to use it however, they state their distributor, Russ Pharmaceuticals, may use it. If this application is ready for approval we will not comment any further about our objection. However, if a N/A letter is issued, we will state our objection to the use of "Lortab" by the distributor (per KJ March 23, 1992).

K.Shah

K Shah
3.27.92

cc;
HFD-638 Jerry Phillips 3/30/92
KShah/JPhillips
hab 3/25/92
89557REV
review

The components and composition of (Hydrocodone Bitartrate 5 mg/5 mL and Acetaminophen 500 mg/15 mL) are stated as follows:

ACTIVE INGREDIENTS	QUANTITY PER 100%	Quantity per 15 mL in mg or mL
Acetaminophen USP	[redacted]	500.0 mg
Hydrocodone Bitartrate USP	[redacted]	5.0 mg
EXCIPIENT		
Alcohol USP	[redacted]	[redacted]
Saccharin Sodium USP	[redacted]	[redacted]
Sucrose NF	[redacted]	[redacted]
Citric Acid USP Anhydrous	[redacted]	[redacted]
Ethyl Maltol	[redacted]	[redacted]
Methylparaben NF	[redacted]	[redacted]
Propylparaben NF	[redacted]	[redacted]
Propylene Glycol USP	[redacted]	[redacted]
Glycerin USP	[redacted]	[redacted]
Sorbitol Solution	[redacted]	[redacted]
FD&C Blue #1	[redacted]	[redacted]
D&C Yellow #10	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Purified Water USP	[redacted]	[redacted]
	100%	15 mL

The [redacted] of the act[redacted] are listed as follows:

[redacted]

Composition & NDS
89557COM.LLT

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING

Original Amendment

DRAFT - Package Insert

DATE OF REVIEW: March 21, 1991

ANDA #: 89-557

NAME OF FIRM: Mikart, Inc.

NAME OF DRUG: Generic: Hydrocodone Bitartrate and Acetaminophen Elixer, 5 mg/500 mg per 15 mL

DATE OF SUBMISSION: February 12, 1991

COMMENTS:

Insert: Satisfactory in draft

However, before preparing final printed labeling please make the following minor editorial change:

ADVERSE REACTIONS, Respiratory Depression

Line 1- lower case "b" in birtartrate.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm prepare and submit final printed insert labeling. We await the submission of final printed container labels.

3. We await the firms response concerning the proposed distributor proprietary name, Lortab Elixir.

4. Chemist:

   See review dated February 18, 1991, for comments on the draft 1 gallon container label.

5. FOR THE RECORD

   A. Russ Pharmaceuticals is the primary distributor of this product.

   B. [redacted]

K.Shah

K Shah

REVIEW OF PROFESSIONAL LABELING

Original Amendment

DRAFT - Container Label

DATE OF REVIEW: February 18, 1991

ANDA #: 89-557

NAME OF FIRM: Mikart, Inc.

NAME OF DRUG: Generic: Hydrocodone Bitartrate and Acetaminophen Elixir, 5 mg/500 mg per 15 mL.

DATE OF SUBMISSION: January 17, 1991

COMMENTS:

Container: Satisfactory in draft for [redacted] However, we encourage you to include an asterisk after hydrocodone in the established name as requested in item 1. II. B. of our letter dated December 19, 1989.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their [redacted] container labels, then prepare and submit final printed labels.

Yana Mille

Yana Mille

cc:
HFD-638
YMille
np/2-22-1991
89557
Review

yf Mille 2/25/91

REVIEW OF PROFESSIONAL LABELING

Orig. Amendment

DRAFT - Container Labels, Package Insert Labeling

DATE OF REVIEW: 5/3/90

ANDA #: 89-557 NAME OF FIRM: Mikart, Inc.

NAME OF DRUG:

Generic: Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL.

DATE OF SUBMISSION: 2/14/90

COMMENTS:

1. General Comments

   A. We note that you have agreed to withdraw the proprietary name, Lortab Elixir. However, you have now indicated that you wish to retain the right for the name in question to be used by a distributor of this product. We do not find this acceptable. We are opposed to the use of this proprietary name by any firm for the reasons stated in our letters dated June 17, 1987 and July 21, 1988. We have contacted the Office of Compliance concerning the use of a proprietary name which has previously been deemed objectionable. We must again ask you to commit that this name will not be used by your firm or by any of your distributors for this product.

   B. We recognize your commitment that Russ Pharmaceuticals, Inc. will be the primary distributor for this product.

2. Container Labels - Satisfactory in draft for 30 mL, 4 fl oz, and 1 pint.

   A. However, we encourage you to include an asterisk after hydrocodone in the established name as requested in item 1.II.B. in our letter dated December 19, 1989.

   B. We note that you have not submitted a revised ——— container label. Do you still intend to use this package size for ——— as you originally indicated? We await your response.

withdrawn 3/3/88 per firm's 1/7/91 letter 2/14/91

3. Insert Labeling - Not Satisfactory

   A. WARNINGS

      Paragraph 3, line 2 - ...diagnosis or (rather than clinical...

   B. HOW SUPPLIED

      You have submitted a draft container label for a 30 mL package size yet this size does not appear in this section. Please comment. We cannot request final printed labeling until this issue is resolved.

withdrawn per 3/3/92 firm's 1/17/91 letter YM 2/18/91

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their package insert labeling, then prepare and submit final printed labels and draft insert labeling for our review and comment.

3. Chemist

   Please be aware that the firm has now submitted a draft container label for a 30 mL package size. They have also dropped the container label. (See the comment B under container labels).

1/17/91 NN

draft labels submitted

Yana Mille
Yana Mille

cc: HFD-638 Y. Mille 5/9/90
YMille/TPoux
ms: 5/4/90 (4505m)

5/9/90

REVIEW OF PROFESSIONAL LABELING

Orig. Amendment

DRAFT - Container Labels, Package Insert Labeling

DATE OF REVIEW: 9-28-89

ANDA #: 89-557 NAME OF FIRM: Mikart, Inc.

NAME OF DRUG: Generic: Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg per 15 mL

DATE OF SUBMISSION: 8-28-89

COMMENTS:

1. General Comments

   A. We recognize your withdrawal of the proprietary name, Lortab Elixir, and consider it to be a commitment that this proprietary name will not be used by your firm or by any of your distributors for this product.

   B. In reviewing the application we were unable to find a statement from you indicating that Russ Pharmaceuticals, Inc. will be the sole distributor of this product. We do not, generally, review or approve distributor labels or labeling. However, if you commit to Russ Pharmaceuticals being the sole distributor an exception can be made.

      We will provide comment on the labels and labeling since the comments apply without consideration for the distributor.

2. Container Labels - Not Satisfactory

   A. Include a prominent expression of product strength directly beneath the established name.

      5 mg/500 mg per 15 mL

   B. We encourage the inclusion of an asterisk(*) after "Hydrocodone" in the established name and before the warning in the contents statement.

   C. You indicated in your submission dated April 17, 1989 that the ——— package size is not a marketed package size but is intended for ———. Under the circumstances this package size should not be included in the insert labeling, however, if you should change your mind and decide to market ——— containers the HOW SUPPLIED section of the insert must be revised.

We would also like to remind you of the need to:

1. provide packaging and labeling supplements
2. address all the issues raised in 21 CFR 201.150(a)(2).

prior to repackaging this product in an unapproved package size.

Package Insert - Not Satisfactory

A. DESCRIPTION

Penultimate Paragraph - The final word should be "which" (rather than ——.

B. CLINICAL PHARMACOLOGY

Paragraph 2, lines 3 and 4 - The numeral and unit of measurement should appear on the same line if at all possible.

C. PRECAUTIONS

1. Paragraph 2 - Line 4 should end in a semicolon(;) rather than a ——
2. Paragraph 8, line 8 - 0.7 (rather than ——

D. ADVERSE REACTIONS

Final Paragraph, sentence 1 - Delete ——————

E. DRUG ABUSE AND DEPENDENCE

Paragraph 1, line 2 - Substances (plural)

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then prepare and submit draft copy for our review and comment. We can not request final printed labels or labeling until the issue discussed in item B under General Comments is resolved.

Y. Mille 10/12/89

Yana Mille

Yana Mille

cc: YMille/TPoux/sb/10/6/89
8386A pg: 12-13 /REV. OF PROF. LBL.

REVIEW OF PROFESSIONAL LABELING

Orig. Amendment; DRAFT-Package Insert Labeling

DATE OF REVIEW: November 8, 1988

ANDA #: 89-557 NAME OF FIRM: Mikart, Inc

NAME OF DRUG: Trade: LORTAB ELIXIR
Generic: Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg per 15 mL

DATE OF SUBMISSION: September 13, 1988

COMMENTS:

1. General Comment:

   A. We await your submission of another proprietary name for this product.

   B. Please explain the use of the ——— package size. Is it to be a marketed package size? If so, it should then be listed in the insert and container labels should be submitted. Is it intended for use as a bulk container? If so, why is it needed? It is our understanding that there are no longer any plans to package this product in unit dose cups.

2. Package Insert Labeling

   The text of the package insert labeling is satisfactory with the exception of items 1. A and B (above). We can not request final printed labels or labeling until these issues are resolved.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

Y. Mille 11/10/88

Yana Mille

Yana Mille

cc:
HFD-238
YMille/TPoux/je/11-8-88
rpl
8076A/pg 1

REVIEW OF PROFESSIONAL LABELING
Orig. Amendment
Container Labels
Package Insert Labeling

DATE OF REVIEW: 5/23/88

ANDA #: 89-557 NAME OF FIRM: Mikart, Inc.

NAME OF DRUG: Trade: LORTAB ELIXIR
Generic: Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL.

DATE OF SUBMISSION: 2/5/88 and 3/3/88

COMMENTS:

1. General Comments

We have considered your comments concerning the use of the root word Lortab, which includes "tab" as a part of the proprietary name for a liquid dosage form. We submitted your comments to the FDA Labeling and Nomenclature Committee and asked for their recommendations. They were in complete agreement with our initial comment that it is inappropriate to include "tab" as part of the name of a liquid preparation. Please suggest another name.

2. A. 1 Pint Container Labels - Not Satisfactory

See comment 1.

B. Bulk Container Label - Not Satisfactory

See comment 1.

3. Package Insert Labeling - Not Satisfactory

A. See comment 1.

B. ADVERSE REACTIONS

Final Paragraph - Sentence 1 should read:

...the brain stem respiratory center.

C. OVERDOSAGE

Acetaminophen - Divide paragraph 2 into two paragraphs. The second paragraph begins with "Early symptoms."

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then prepare and submit draft copy for our review and comment.

3. FOR THE RECORD

   For comments on the proprietary name see review dated 5/23/88 for ANDA 89-759.

4. Chemist

   Is the "written agreement" submitted in response to labeling comment 1.E. acceptable?

Firm withdrew unit dose ∴ bulk pkg. cc not needed

Yana Mille

Yana Mille

cc: Y Mille 5/25/88 B 6/2/88
DUP
YMille/TPoux/gp/5/24/88
1269g P. 12-13

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING

Orig. Amendment; Unit Dose, Carton and Container Labels,
Package Insert Labeling/DRAFT

DATE OF REVIEW: February 26, 1987

ANDA/NDA#: 89-557 NAME OF FIRM: Russ Pharmaceuticals, Inc.

NAME OF DRUG: Trade: LORTAB ELIXIR
Generic: Hydrocodone Bitartrate and Acetaminophen
(5 mg/500 mg per 15 mL)

DATE OF SUBMISSION: January 30, 1987

COMMENTS:

General Comment

and have reviewed this matter with the Division of Drug Advertising and Labeling.

We have considered your comments relating to LORTAB ELIXIR and have the following remarks:

1) You state that LORTAB is a trade name used to identify the line of products distributed by Russ Pharmaceuticals Incorporated. You do not make specific comment whether different drug entities are involved, or whether we are only talking about hydrocodone bitartrate and acetaminophen.

2) Your justification on using LORTAB ELIXIR as a trade name is not compelling. While you state that there have been no reports of problems associated with this proprietary name, we cannot evaluate this claim since we do not know the marketing history of LORTAB ELIXIR, or any other LORTAB product.

3) Your claim that the prescribers of LORTAB products know the line well is immaterial. The Agency cannot be expected to evaluate educational efforts of a firm in explaining a misleading trade name. Further, the Agency believes precedent is an important feature of consistent decisions in this area of regulatory oversight. To permit the name you propose could be viewed as Agency agreement with this type of proprietary name.

4. In summary, we believe the proprietary name LORTAB ELIXIR is undesirable because the core name implies tablets, yet the dosage form is not a tablet.

Unit Dose - Satisfactory

However, see the General Comment concerning the proprietary name.

Carton - Not Satisfactory

A. Usual Dosage - adult (spelling)

B. See the General Comment concerning the proprietary name.

C. See comment B. under Insert.

Container Labels: Not

A. Container Label - Satisfactory

~~However~~, 1. See the General Comment concerning ther proprietary name.
2. See comment B under Insert.

B. Bulk Container Label

1. The firm should supply evidence of a proposed "written agreement" which will address all the issues raised in 21 CFR 201.150(a)(2). We are especially interested in the plan for transfer of labels and labeling to the repacker.

2. We do not believe the sentence following the Federal CAUTION statement should appear on the label. This should instead be a part of the above cited written agreement.

3. The approximate volume in milliliters should be noted on the label.

4. The storage recommendations for the bulk container may well be more restrictive than the marketed package labels. We also suggest that conditions of relative humidity be noted.

5. See the General Comment concerning the proprietary name.

Insert - Not Satisfactory

A. TITLE:

See the General Comment concerning the proprietary name.

C. ~~B~~. HOW SUPPLIED:

1. The recommendations to the pharmacist on the type of container to use for dispensing should appear in a section that is separate from the storage recommendations.

2. Include an expression of product strength based on 15 mL.

RECOMMENDATIONS:

1. Inform the firm of above comments.

2. Request the firm revise their unit dose, carton and container labels and package insert labeling, then prepare and submit draft copy for our review and comment. Do not prepare final printed insert labeling until the Bio data has been found acceptable and ~~we~~ we have had a chance to review and comment.

3. Chemist

Has sufficient quantitative information been submitted to determine whether this product is a syrup, oral solution or elixir.?

Yana Mille

HFN-238/ Mille 3/13/87
YMille/KJohnson/shd/3-12-87
3333A/pg 5-6

2-16-87

The usual adult dosage is one or two tablespoonfuls every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablespoonfuls.

REVIEW OF PROFESSIONAL LABELING

ANDA/DRAFT-Unit Dose Carton, Bulk Package and Container Labels; Package Insert Labeling

DATE OF REVIEW: November 7, 1986

ANDA/NDA#: 89-557 NAME OF FIRM: Russ Pharmaceutical

NAME OF DRUG: Trade: [redacted]
Generic: Hydrocodone Bitartrate and Acetaminophen 5 mg/500 mg per 15 mL

DATE OF SUBMISSION:

COMMENTS:

Unit Dose: Not Satisfactory

A. [redacted]

Please comment.

B. We agree that the USP requires that the amount of active drug be labeled in terms of each 5 mL portion of the liquid. However, as a practical matter, we will allow this unit-dose package to express the amount of drug in terms of the total content since it is a single unit container.

[redacted]

therefore we suggest:

Each 15 mL contains:
etc.

C. You may delete the, [redacted] statement to conserve space.

D. The NDC should appear above the proprietary name, not beneath it.

E. [redacted]

Carton: Not Satisfactory

A. See comment A under Unit-Dose

B. While the expression of strength is required to be stated in terms of active drug per 5 mL, we recognize the reasonableness and need to show the content per 15 mL (as 15 mL is the usual adult dose). Therefore, we propose that following simple table appear on labels and labeling which will reflect both expressions:

	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate (WARNING: May be habit forming)	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7%	7%

(Note: Delete the word " ——— " which appears after alcohol)

C. The symbol for degrees (o) is a supercript not ———

D. We prefer Single dose container (rather than ———

Container: Not Satisfactory

A. Container Label

1. See comment A under Unit Dose

2. See comments B and C under Carton

B. Bulk Container Label

1. Delete " ———

2. Please add the storage recommendations.

Insert: Not Satisfactory

A. DESCRIPTION

See comment A under Unit Dose

B. OVERDOSAGE

1. Hydrocodone, Treatment, Paragraph 1, Line 7 should read:

...naloxone hydrochloride....

2. Acetaminophen, Signs and Symptoms, Paragraph 1, Line 3- overdose (rather than ———

C. HOW SUPPLIED

Storage Recommendations-The symbol for degrees (°) is a supercript not a ———

RECOMMENDATIONS:

1. Inform the firm of above comments.

2. Request the firm revise their unit dose, carton bulk package and container labels and package insert labeling, then prepare and submit draft copy for our review and comment.

3. Chemist

A. Please review the bulk package label. We have made the comments we feel are appropriate (see II under Container). Do you have anything to add?

B. See comment E under unit-dose. If your review reveals Russ Pharmaceutical is not a repackager please let me know.

HFN-238
K.Johnson/Y.Mille/st/11-17-86
2917A Pg 3-5

for Yana Mille

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

NDA: 89-557

DRUG PRODUCT: Hydrocodone Bitartrate and Acetaminophen

FIRM: Mikart Inc.

DOSAGE FORM: Elixir

STRENGTH: [5 mg/500 mg]/15 mL

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form:

Mikart Inc.(2090 Marietta Boulevard, N.W. Atlanta, Ga 30318 (OK). Final pre-approval EER pending (4/15/92).

Manufacturer-Active Ingredients:

[redacted]

Final pre-approval EER pending (4/15/92).

Contract Laboratories:

1. [redacted]

2. [redacted]

Final pre-approval EER pending (4/15/92).

BIO STUDY:

Bio-waiver was granted on 11/18/86.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Sample analyses for [redacted] are not applicable according to DGD policy and guideline (because these drug substances are USP product).

Method validation and sample analysis for the finished dosage product were acceptable by [redacted] on 2-13-92.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol:

Stability protocol was shown on pages 194-196 of 6-15-88 amendment, 1-17-91 amendment and pages 1121-1128 of the 3-9-92 submission.

Expiration date:

24 months expiration date with 3 months challenge (40°C & 75%

R.H.) and 3 months room temperature stability data on invert position for package sizes ——, 4 oz, and 16 oz on lot E91210.

The batch size for lot E91210 is —— The stability data were shown on stability data section of the 3-9-92 submission.

LABELING:

Satisfactory per KShah reviewed on 3-27-92.

STERILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Batch size: —— source of —— USP lot# 91142 and the —— lot # 91040.

Mallinckrodt, Inc for DMF —— was acceptable by Lucia Tang on 1-9-92. Mallinckrodt, Inc for DMF #—— was acceptable by on 4-17-92.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The batch size for the stability batch (lot #E91210) is not the same as bio-waiver batch (Lot K7372). Lot E91210 was manufactured at the request of the FDA Atlanta District Office for the pre-approval inspection for this application. Lot K7372 in original submission was unacceptable.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch is —— (pages 657 of 3-9-92 submission) and has the same manufacturing process as the test batch ——.

CHEMIST: Lucia C. Tang DATE: 4-21-92 4/28/92

SUPERVISOR: Florence Fang DATE: 4/28/92

89557AAP.P/LTang/4-21-92

#1

3. NAME AND ADDRESS OF APPLICANT

Russ Pharmaceuticals, Inc.
P.O. Box 20507
Birmingham, Alabama 35216

6. NAME OF DRUG

Lortab Liquid

7. NONPROPRIETARY NAME

Hydrocodone Bitartrate 5 mg/15 mL
Acetaminophen 500 mg/15 mL

10. PHARMACOLOGICAL CATEGORY

Analgesic/Antitussive

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(s)

DMF — (Mikart)
DMF ———————
DMF ———————

13. DOSAGE FORM(s)

(Syrup/Elixir)?

14. POTENCY

[5 mg/500 mg]/15 mL

15. CHEMICAL NAME AND STRUCTURE

N-(4-hydroxyphenyl)acetamide and 4,5-Epoxy-3 methoxy-17-methylmorphinan-6-one hemipentahydrate

17. COMMENTS

This product was petitioned for ANDA acceptability status, and was determined acceptable as an ANDA application.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable-applicant refers to ———————— This is unacceptable. The review of the application will be deferred until this information is included in the ANDA.

19. REVIEWER:

Bill Marnane 1267

DATE COMPLETED:

12/16/86

APPEARS THIS WAY
ON ORIGINAL

Redacted 3

Page(s) of trade secret and /or confidential commercial information

#2

CHEMIST'S REVIEW ANDA 89-557

3. NAME AND ADDRESS OF APPLICANT
Mikart, Inc.
2090 Marietta Blvd. N.W.
Atlanta, GA 30318

5. ORIGINAL
March 24, 1987

6. NAME OF DRUG
Hydrocodone Bitartrate
and Acetaminophen

7. NONPROPRIETARY NAME
Lortab Elixir

10. PHARMACOLOGICAL CATEGORY
Analgesic and Antitussive

11. HOW DISPENSED
RX

12. RELATED IND/NDA/DMF(s)
89-271, 89-689, 89-698
89-697, 89-699, 89-577

13. DOSAGE FORM(s)
Tablets
Elixir or Liquid

14. POTENCY
[5 mg/500 mg]/15 mL

17. COMMENTS
1. Revise labeling information
2. Revise formulation because the content of Hydrocodone Bitartrate
3. Revise components and composition
4. Revise manufacturing process
5. Revise container/closure system
6. Revise stability data and stability protocol

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable

19. REVIEWER:
Lucia C. Tang

DATE COMPLETED:
10-27-87

11/3/87

APPEARS THIS WAY
ON ORIGINAL

Redacted 3

Page(s) of trade secret and /or confidential commercial information

#3

CHEMIST'S REVIEW ANDA 89-557

NAME AND ADDRESS OF APPLICANT
Mikart, Inc.
2090 Marietta Blvd. N.W.
Atlanta, GA 30318

5. ORIGINAL
March 24, 1987

6. NAME OF DRUG
Hydrocodone Bitartrate and Acetaminophen

7. NONPROPRIETARY NAME
Lortab Elixir

10. PHARMACOLOGICAL CATEGORY
Analgesic and Antitussive

11. HOW DISPENSED
RX

12. RELATED IND/NDA/DMF(s)
89-271, 89-689, 89-698
89-697, 89-699, 89-577

13. DOSAGE FORM(s)
Tablets
Elixir or Liquid

14. POTENCY
[5 mg/500 mg]/15 mL

17. COMMENTS
1. Revise labeling information
2. Revise components and composition
3. Revise manufacturing process
4. Revise stability data

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable

19. REVIEWER:
Lucia C. Tang

DATE COMPLETED:
2-6-89

APPEARS THIS WAY
ON ORIGINAL

Redacted 3

Page(s) of trade secret and /or confidential commercial information

CHEMIST'S REVIEW ANDA 89-557

3. NAME AND ADDRESS OF APPLICANT
Mikart, Inc.
2090 Marietta Blvd. N.W.
Atlanta, GA 30318

5. ORIGINAL
March 24, 1987

6. NAME OF DRUG
Hydrocodone Bitartrate and Acetaminophen

7. NONPROPRIETARY NAME
Lortab Elixir

10. PHARMACOLOGICAL CATEGORY
Analgesic and Antitussive

11. HOW DISPENSED
RX

12. RELATED IND/NDA/DMF(s)
89-271, 89-689, 89-698
89-697, 89-699, 89-577

13. DOSAGE FORM(s)
Tablets
Elixir or Liquid

14. POTENCY
[5 mg/500 mg]/15 mL

17. COMMENTS
1. Revise labeling information
3. Revise components and composition
4. Revise manufacturing process
5. Revise container/closure system
6. Revise stability data and stability protocol

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable

19. REVIEWER:
Lucia C. Tang

DATE COMPLETED:
10-27-87

7/14/88

APPEARS THIS WAY
ON ORIGINAL

Redacted 3

Page(s) of trade secret and /or confidential commercial information

A 5

1. CHEMIST'S REVIEW NO. 6

2. ANDA #

89-557

3. NAME AND ADDRESS OF APPLICANT

Mikart, Inc.
2090 Marietta Blvd. N.W.
Atlanta, GA 30318

5. SUPPLEMENT(s)

March 24, 1987

6. TRADE NAME

Hydrocodone Bitartrate
and Acetaminophen

9. AMENDMENTS AND OTHER DATES:

Firm:
1. September 15, 1986 with original application from Russ.
2. Jan 30, 1987 with draft labeling.
3. June 11, 1987 with transfer ownship from Russ to Mikart (effective date June 4, 1987).
4. June 16, 1987 with Mikart's agreement for the processing, control or marketing of the ANDA.
5. Sept. 4, 1987 with Mikart's DMF authorization
6. July 11, 1987 with original application from Mikart
7. June 15, 1988 with information regarding stability and container/closure system from Mikart
8. June 21, 1988 with amendment
9. Sept. 30, 1988 with amendment
10. Nov. 18, 1988 with transfer ownership
11. April 17, 1988 with admendment
12. August 28, 1988 with draft labeling for deleting Lortab Elixir name

FDA:
1. Oct. 15, 1986 with acknowledgement to Russ
2. Nov. 18, 1986 with Biowaiver granted.
3. Dec. 23, 1986 with 1st deficiency letter to Russ
4. June 17, 1987 with 2nd deficiency letter to Russ
5. Nov. 4, 1987 with 3rd deficiency letter to Mikart
6. Nov. 21, 1988 with 4th deficiency letter to Mikart
7. Feb. 14, 1988 with 5th deficiency letter to Mikart

10. PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

89-271, 89-689, 89-698
89-697, 89-699, 89-577

13. DOSAGE FORM

Elixir

14. POTENCY

[5 mg/500 mg]/15 mL

17. COMMENTS

1. Revise labeling information
2. Revise components and composition
3. Revise manufacturing process
4. Revise stability data

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

Lucia C. Tang

DATE COMPLETED:

11-28-89

Lucia C. Tang 12/11/89

12/14/89

APPEARS THIS WAY
ON ORIGINAL

Redacted 4

Page(s) of trade secret and /or confidential commercial information

6
1-1491

1. CHEMIST'S REVIEW NO. 7

2. ANDA #

89-557

3. NAME AND ADDRESS OF APPLICANT

Mikart, Inc.
2090 Marietta Blvd. N.W.
Atlanta, GA 30318

5. SUPPLEMENT(s)

NA

6. TRADE NAME

Hydrocodone Bitartrate
and Acetaminophen

9. AMENDMENTS AND OTHER DATES:

Firm:

1. September 15, 1986 with original application from Russ.
2. Jan 30, 1987 with draft labeling.
3. June 11, 1987 with transfer ownship from Russ to Mikart (effective date June 4, 1987).
4. June 16, 1987 with Mikart's agreement for the processing, control or marketing of the ANDA.
5. Sept. 4, 1987 with Mikart's DMF authorization
6. July 11, 1987 with original application from Mikart
7. June 15, 1988 with information regarding stability and container/closure system from Mikart
8. June 21, 1988 with amendment
9. Sept. 30, 1988 with amendment
10. Nov. 18, 1988 with transfer ownership
11. April 17, 1988 with amendment
12. August 28, 1988 with draft labeling for deleting Lortab Elixir name
13. 2-14-90 with amendment and draft labeling
14. 8-24-90 with amendment

FDA:

1. Oct. 15, 1986 with acknowledgement to Russ
2. Nov. 18, 1986 with Biowaiver granted.
3. Dec. 23, 1986 with 1st deficiency letter to Russ
4. June 17, 1987 with 2nd deficiency letter to Russ
5. Nov. 4, 1987 with 3rd deficiency letter to Mikart
6. Nov. 21, 1988 with 4th deficiency letter to Mikart
7. Feb. 14, 1988 with 5th deficiency letter to Mikart

10. PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

89-577, 81-051

13. DOSAGE FORM

Elixir

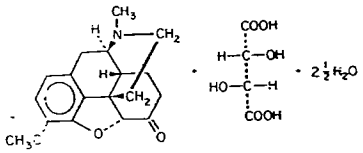
14. POTENCY

[5 mg/500 mg]/15 mL

15. CHEMICAL NAME AND STRUCTURE

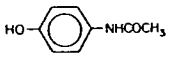
Hydrocodone Bitartrate
4,5 x-Epoxy-methoxy-17-methylmophinan-6-one tartrate (1:1) hydrate (2:5)
CAS # [34195-34-1; 6190-38-1]

Hydrocodone Bitartrate



Acetaminophen
4'-Hydroxyacetanilide
CAS # [103-90-2]

Acetaminophen



17. COMMENTS

1. Revise labeling information(see labeling issue letter)

2. Revise stability stability protocol

3. The container/closure system in chemistry review are correct. However the the container/closure system in draft labeling submission dated 2-14-91 are incorrect according to firm's conversation with L. Tang dated January 16, 1991. Firm should provide correct labeling information and clarify the container/closure system.

4. We acknowledge that the intended production batch of ——— has been withdrawn from the application. The proposed production batcch size has been changed from ——— to

5. For finished product:

   a. the certificate of analysis of the finished product on page 41 of February 14, 1990 amendment is imcomplete. The sources of the active ingredients, the product description and packaging lot # must be included.

   b. Submit the certificates of analysis of the finished product from each of packaging lot (e.g., each of container/closure system).

6. For stability protocol:

   a. All future accelerated stability studies, the conditions are to be 40°c for liquid, syrup and injection. For room temperature stability studies, actual temperature and humidity must be monitored and reported.

   b. All sizes of the container/closure system must be included in stability studies.

   c. Since you have agreed that a supplement will be submitted for rework processes, the general stability protocol for reworked batches submitted in the original application should be deleted.

7. For stability data:

   We note that the stability data for one oz was submitted in your amendment dated February 14, 1990. However, no information for the container/closure system was provided in the original submission. Please withdraw or delete.

8. We cannot locate your environmental impact statement from Mikart. The environmental impact analysis submitted on page 181 of original submission is from Russ Pharmaceutical, Inc. Please submit the current environmental impact from Mikart, Inc.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 1-14-91

Lucia C. Tang 1/23/91

APPEARS THIS WAY
ON ORIGINAL

Redacted 5

Page(s) of trade secret and /or confidential commercial information

Stw 4/28/98

9-10-91

1. CHEMIST'S REVIEW NO. 7

2. ANDA #

89-557

3. NAME AND ADDRESS OF APPLICANT

Mikart, Inc.
2090 Marietta Blvd. N.W.
Atlanta, GA 30318

5. SUPPLEMENT(s)

NA

6. TRADE NAME

Hydrocodone Bitartrate
and Acetaminophen

9. AMENDMENTS AND OTHER DATES:

Firm:

1. September 15, 1986 with original application from Russ.
2. Jan 30, 1987 with draft labeling.
3. June 11, 1987 with transfer ownership from Russ to Mikart (effective date June 4, 1987).
4. June 16, 1987 with Mikart's agreement for the processing, control or marketing of the ANDA.
5. Sept. 4, 1987 with Mikart's DMF authorization
6. July 11, 1987 with original application from Mikart
7. June 15, 1988 with information regarding stability and container/closure system from Mikart
8. June 21, 1988 with amendment
9. Sept. 30, 1988 with amendment
10. Nov. 18, 1988 with transfer ownership
11. April 17, 1988 with amendment
12. August 28, 1988 with draft labeling for deleting Lortab Elixir name
13. 2-14-90 with amendment and draft labeling
14. 8-24-90 with amendment
15. 2-12-91 with responding 6th deficiency letter (current)
16. 8-19-91 with contract lab (current)

FDA:

1. Oct. 15, 1986 with acknowledgement to Russ
2. Nov. 18, 1986 with Bio-waiver granted.
3. Dec. 23, 1986 with 1st deficiency letter to Russ
4. June 17, 1987 with 2nd deficiency letter to Russ
5. Nov. 4, 1987 with 3rd deficiency letter to Mikart
6. Nov. 21, 1988 with 4th deficiency letter to Mikart

7. Feb. 14, 1988 with 5th deficiency letter to Mikart
8. 2-4-91 with 6th deficiency letter to Mikart

10. PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

89-577, 81-051

13. DOSAGE FORM

Elixir

14. POTENCY

[5 mg/500 mg]/15 mL

15. CHEMICAL NAME AND STRUCTURE
Hydrocodone Bitartrate

4,5 x-Epoxy-methoxy-17-methylmophinan-6-one tartrate (1:1) hydrate (2:5)
CAS # [34195-34-1; 6190-38-1]

Acetaminophen

4'-Hydroxyacetanilide
CAS # [103-90-2]

APPEARS THIS WAY
ON ORIGINAL

17. COMMENTS

1) Revise labeling information (see labeling issue letter)

2) We await your response concerning the proposed distributor proprietary name, Lortab Elixir.

3) We note you state the _____ container is not a marketed package size; however, you have submitted stability data for this package size. Please clarify.

4) We were informed on June 13, 1991 by Investigations Branch at Atlanta District Office that a sample for the finished product for this ANDA was not collected. We understand you have committed to make a new batch to support this application using new equipment and new procedures.

5) You are to manufacture a batch of the drug product at least — of the regular commercial production batch using the new equipment and new procedures. Please submit the executed batch record, finished product specifications and test data and 3-month accelerated stability data.

6) Please indicate your intended production batch sizes. Please submit blank batch records based on the new manufacturing procedures and equipment.

7) We acknowledge that _____ and _____ have been deleted as contract facilities from this application on your amendment dated August 19, 1991.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 9-10-91

9/18/91

9/19/91

Redacted 5

Page(s) of trade secret and /or confidential commercial information

File this Copy

1. CHEMIST'S REVIEW NO. ~~9~~ 8

2. ANDA #

89-557

3. NAME AND ADDRESS OF APPLICANT

Mikart, Inc.
2090 Marietta Blvd. N.W.
Atlanta, GA 30318

4. AF NUMBER

Vicodin from Knoll Pharmaceutical Company

5. SUPPLEMENT(s)

NA

6. TRADE NAME

Hydrocodone Bitartrate
and Acetaminophen

9. AMENDMENTS AND OTHER DATES:

Firm:

1. September 15, 1986 with original application from Russ.
2. Jan 30, 1987 with draft labeling.
3. June 11, 1987 with transfer ownership from Russ to Mikart (effective date June 4, 1987).
4. June 16, 1987 with Mikart's agreement for the processing, control or marketing of the ANDA.
5. Sept. 4, 1987 with Mikart's DMF authorization
6. July 11, 1987 with original application from Mikart
7. June 15, 1988 with information regarding stability and container/closure system from Mikart
8. June 21, 1988 with amendment
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12. August 28, 1988 with draft labeling for deleting Lortab Elixir name
13. 2-14-90 with amendment and draft labeling
14. 8-24-90 with amendment
15. 2-12-91 with responding 6th deficiency letter
16. 8-19-91 with contract lab
17. **10-9-91:NC**
18. **1-22-92:NC**
19. **1-27-92:NC**
20. **3-9-92: amendment**
21. **3-26-92:NC for "Lortab"**

4-24-92: amendment, withdraws ——— pgs

FDA:

1. Oct. 15, 1986 with acknowledgement to Russ
2. Nov. 18, 1986 with Bio-waiver granted.
3. Dec. 23, 1986 with 1st deficiency letter to Russ
4. June 17, 1987 with 2nd deficiency letter to Russ
5. Nov. 4, 1987 with 3rd deficiency letter to Mikart
6. Nov. 21, 1988 with 4th deficiency letter to Mikart
7. Feb. 14, 1988 with 5th deficiency letter to Mikart
8. 2-4-91 with 6th deficiency letter to Mikart
9. 9-23-91 with 7th deficiency letter to Mikart
10. 2-13-92 with OK on method validation
11. 4-15-92 with pre-approval EER

10. PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

89-577. 81-051
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM

Elixir

14. POTENCY

[5 mg/500 mg]/15 mL

15. CHEMICAL NAME AND STRUCTURE

Hydrocodone Bitartrate

$C_{18}H_{21}NO_3 . C_4H_6O_6 . 2\frac{1}{2}H_2O$

4,5 x-Epoxy-methoxy-17-methylmophinan-6-one tartrate (1:1) hydrate (2:5)
CAS # [34195-34-1; 6190-38-1]

Acetaminophen

$C_8H_9NO_2$

Acetamid, 4'-Hydroxyacetanilide
CAS # [103-90-2]

17. COMMENTS

1. The use of the name "Lortab"is still unresolved, Mikart proposes not to use it however, they state their distributor, Russ Pharmaceuticals, may use it. See labeling comments (If this application is ready for approval we will not comment any further about our objection per KJ 3-23-92).

2) We acknowledge that _____ and _____, have been deleted as contract facilities from this application on your amendment dated August 19, 1991.

3) Lot E91210 was manufactured at the request of the FDA Atlanta District Office for the pre-approval inspection for this application. Lot K7372 in original submission was unacceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 4-16-92

4/28/92

4/28/92

APPEARS THIS WAY
ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557

BIOEQUIVALENCE REVIEW(S)

11/12/86

Hydrocodone Bitartrate/Acetaminophen Syrup
Lortab Liquid,
5 mg/500 mg per 15 ml Syrup
ANDA #89-557
Reviewer: Beatrice Chen
Wang #8943e

Russ Pharmaceuticals, Inc.
Birmingham, Alabama
Submission Date:
September 15, 1986

Review of a Request for Waiver of In Vivo Bioequivalence Study

The firm has submitted a request for waiver of an in vivo bioequivalence study for its Hydrocodone Bitartrate/Acetaminophen 5 mg/500 mg per 15 ml Syrup. The drug product is an oral liquid form with the following composition:

Lortab Liquid

Ingredient	Per 15 ml
Acetaminophen USP	500 mg
Hydrocodone bitartrate USP	5.0 mg*
Alcohol USP	
Saccharin Sodium USP	
Sucrose NF	
Citric Acid USP Anhydrous	
Ethyl Maltol	
Methylparaben NF	
Proplyparaben NF	
Propylene Glycol USP	
Glycerin USP	
Sorbitol Solution USP	
FD & C Blue #1	
D & C Yellow #10	
Purified Water USP	

* Hydrocodone Bitartrate used

Comments:

Fifteen ml of test syrup contains the same amount of active ingredients as those in the tablet form of Viscodin which is coded "AA" in the "Approved Drug Product with Therapeutic Equivalence Evaluations." According to the Waiver Policy of the Division of Bioequivalence (May 5, 1986), the test syrup can be waived of an in vivo bioequivalence study. The test syrup also satisfies CFR 320.22 (b)(5) in that it contains no inactive ingredient that is known to significantly affect the absorption of the active ingredients. Therefore, the waiver of in vivo bioequivalence study should be granted.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Russ Pharmaceuticals, Inc. demonstrates that Hydrocodone Bitartrates/Acetaminophen 5 mg/500 mg per 15 ml syrup falls under 21 CFR Section 320.22 (b)(5) and the Waiver Policy of the Division of Bioequivalence (May 5, 1986) of the Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the combination syrup product, 5 mg/500 mg per 15 ml, is granted. From the bioequivalence point of view, the firm has met the in vivo bioequivalence requirements. Accordingly, an in vivo bioequivalence study does not need to be undertaken.

Beatrice P. Chen
Beatrice Chen, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED BY RMHATRE
FT INITIALED BY RMHATRE Ramakant M. Mhatre 11/12/86

BChen/ngo/#8943e/11/4/86

cc: ANDA 89-557 original, HFN-230(2), HFN-258 (BChen, Mhatre), HFN-200 (Hare), HFN-223 (Shah-FOI-2), drug file

APPEARS THIS WAY
ON ORIGINAL

3.1

MAY 6 1992

Acetaminophen/Hydrocodone Bitartrate
500 mg/5 mg per 15 mL, Elixir
ANDA #89-557
Reviewer: F. Nouravarsani
89557W.688

Mikart, Inc.
Atlanta, GA
Submission Date:
June 09, 1988

Review of a Waiver Request

Mikart, Inc. has requested a waiver of bioavailability study requirements for its Test Product, Lortab Elixir, Acetaminophen/ Hydrocodone Bitartrate, 500 mg/5 mg per 15 mL Elixir under CFR 21 320.22 (b)(5). The firm has an approved suitability citizen petition for its Test product as a new dosage form (Docket #84P-0391/CP, dated July 02, 1985).

The firm has reformulated the Test product to use 5.0 mg per 15 mL of Hydrocodone Bitartrate instead of 5.556 mg per 15 mL. This change was previously recommended by the agency. The formulation of the Test product is summarized in attached Table 1.

Deficiency: None

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Mikart Inc. demonstrates that Acetaminophen/ Hydrocodone Bitartrate, 500 mg/5 mg per 15 mL, Elixir falls under CFR 21 section 320.22 (b)(5). The Division of Bioequivalence recommends that the waiver of bioequivalence study requirements be granted.

F. Nouravarsani

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE Ramakant M. Mhatre

FNouravarsani/05-01-92/89557W.688

CC: ANDA #89-557, HFD-630, HFD-604 (Hare), HFC-130 (JAllen), HFD-658 (Mhatre, Nouravarsani), Drug File.

Table 1

COMPOSITION STATEMENT
LORTAB ELIXIR
June, 1988

The composition of Lortab Elixir as reformulated per FDA recommendation is

ACTIVE INGREDIENTS	Quantity per 100 %	Quantity per 15 mL in mg or mL
Acetaminophen USP		500.0 mg
Hydrocodone Bitartrate USP		5.0 mg
Alcohol USP (equivalent to alcohol		
EXCIPIENTS		
Saccharin Sodium USP		
Sucrose NF		
Citric Acid USP Anhydrous		
Ethyl Maltol		
Methylparaben NF		
Propylparaben NF		
Propylene Glycol USP		
Glycerin USP		
Sorbitol Solution		
FD&C Blue #1		
D&C Yellow #10		
	%	
Purified Water USP		
	100 %	15 mL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557

ADMINISTRATIVE DOCUMENTS

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

89-557

DATE APPROVAL LETTER ISSUED

TO:

Press Relations Staff (HFI-40)

FROM:

[X] Bureau of Drugs

[ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION

[ ] ORIGINAL NDA [ ] SUPPLEMENT TO NDA [X] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY

[X] HUMAN [ ] VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG

Hydrocodone Bitartrate and Acetaminophen Elixir, 5 mg/500 mg per 15 mL

DOSAGE FORM

Elixir

HOW DISPENSED

[X] RX [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s). If amount is declared on label.)

Active Ingredients	Quantity per 15 mL in mg
Acetaminophen USP,	500.0 mg
Hydrocodone Bitartrate USP	5.0 mg

NAME OF APPLICANT (Include City and State)

Mikart, Inc
2090 Marietta Blvd., N.W.
Atlanta, GA 30318

APPEARS THIS WAY ON ORIGINAL

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Analgesic and Antitussive

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: Lucia C. Tang

DATE: 4/28/92

FORM APPROVED BY

NAME: Florence Fang

DATE:

FORM FO 1642 (1/75)

PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office)	FROM:
DIV. OF DRUG ADVERTISING & LABELING HFN 240	DIV. OF GENERIC DRUG HFN-230

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/3/87		89-557		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydrocodone Bitartrate/Acetaminophen Elixir			

NAME OF FIRM
RUSS PHARMACEUTICALS

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW	☐ CHEMISTRY
END OF PHASE II MEETING	☐ PHARMACOLOGY
CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
PROTOCOL REVIEW	☐ OTHER
OTHER	

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- F E IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Russ Pharmaceuticals is proposing the name (Page 1) Lortab Elixir for this product. See item #2. of our letter dated 12/23/86 for our initial reaction to the proposed product name. Then see the firms response (Page 2). Kindly review and comment upon our proposed response to the firm (Page 3)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
Yana Mille	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89-557

CORRESPONDENCE

6.1

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

NEW CORRESP

April 24, 1992

RECEIVED

MAY 1 1992

GENERIC DRUGS

Dr. Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
HFD-637, Room 132
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
(5 mg/500 mg per 15 mL)
Amendment to a pending application

Dear Dr. Williams:

As per our telephone conversations of this week with Chemistry reviewer, Lucy Tang, attached please find the revised stability protocol with the following changes: 1) requirements for humidity in accelerated storage conditions have been deleted. 2) room temperature conditions have been changed to specify 25-30°C. Also, we are hereby withdrawing all references made with respect to the ——— size packaging container in the labeling, packaging components, and stability sections. Furthermore, we are withdrawing any references made in the stability section to lot number 910314E, packaged in the 16 oz container with the ———

Thank you for your continued cooperation in the review of this application. Please feel free to contact us if you require any additional information.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald
Vice-President

CBM/cc

5-4-92

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

KING & SPALDING
1730 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, DC
20006-4706

202/737-0500
TELECOPIER: 202/626-3737

191 PEACHTREE STREET
ATLANTA, GEORGIA 30303-1763
TELEPHONE: 404/572-4600
TELEX: 54-2917 KINGSPALD ATL
TELECOPIER: 404/572-5100

745 FIFTH AVENUE
NEW YORK, NY 10151
TELEPHONE: 212/758-8700
TELECOPIER: 212/593-3673

March 26, 1992

ORIG NEW CORRES

RECEIVED

MAR 2 6 1992

GENERIC DRUGS

By Messenger

Dr. Roger Williams, Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place, Room 286
Metro Park North
Rockville, MD 20855

Re: ANDA # 89-557: Lortab Elixir
REQUEST FOR MEETING

Dear Dr. Williams:

I am writing on behalf of Whitby Pharmaceuticals, on whose behalf Mikart, Inc. has submitted the above referenced abbreviated new drug application. Mikart is the contract manufacturer for Whitby; Whitby's is the only product that will be made under this ANDA. (I am also counsel to Mikart.)

The application, so far as we can tell, is ready for approval. The preapproval inspection was conducted by Investigator Robert Coleman from the Atlanta District Office on February 28, 1992. At the conclusion of the inspection, he said he intended to recommend approval.

The only outstanding issue is the name of the product, "Lortab® Elixir."

In 1980, Russ Pharmaceuticals, which was purchased by Whitby in 1989, created a line of hydrocodone bitartrate (HCB)/ acetaminophen (APAP) products named "Lortab®," which is a registered trademark. Currently there are three approved products: "Lortab® 2.5/500," "Lortab® 5/500," and "Lortab® 7.5/500." Whitby anticipates approval of a 10 mg HCB/500 mg APAP product imminently which will be marketed as "Lortab® 10/500."

"Lortab®," in other words, is the name used for a line of HCB/APAP products with different strengths of HCB in combination with 500 mg APAP. The products are detailed in 48 of the fifty states.

"Lortab® Elixir 5/500," which is the subject of this letter, is a 5 mg HCB/500 mg APAP per tablespoon combination. (Other applications are pending for "Lortab® Elixir 7.5/500" (ANDA 81-051) and "Lortab® Syrup 5/500" (ANDA 98-759).)

Correspondence regarding this ANDA and the other liquid product ANDAs from the Division of Generic Drugs objected to the use of the proprietary name, "Lortab®," on a liquid product "because the core name implies tablets, yet the dosage form is not a tablet."

> We believe it is inappropriate to reference the tablet dosage form in the proprietary name of a liquid product. We believe that confusion will likely occur from prescriptions and hospital orders when the description is not precise as is often the case. Carried further, the results of this name can be predicated to require needless confirmation communications between physician, nurse and pharmacist and also result in medication errors. Further, the Agency believes precedent is an important feature of consistent decisions in this area of regulatory oversight. To permit the proposed name could be viewed as Agency agreement with this type of proprietary name.

On March 9, 1992 Ms. Cerie McDonald of Mikart spoke with Mr. Kent Johnson about the name issue and reported to Whitby that Mr. Johnson remains adamantly opposed to use of the "Lortab®" name with a liquid product.

Dr. Williams, this is difficult for us to comprehend.

1. The name of the product is not confusing.

The name of this product is "Lortab® Elixir," not "Lortab®." I cannot imagine why a physician or pharmacist would look to one syllable of the first word of a product's two word proprietary name to discern its dosage form, especially when the second word in the proprietary name states the dosage form, "Elixir."

2. Medication errors will not occur.

Furthermore, a prescription, whether oral or written, includes not only the name of the drug, but also directions for use. Lortab® Elixir's directions for use are in terms of tablespoonsful, making perfectly clear that the product is a liquid and not a tablet. Thus, even if a physician omitted "Elixir" in his or her prescription, the direction to take one tablespoonful every four hours would either result in Lortab® Elixir being dispensed or trigger a request for clarification, thereby preventing a medication error. Having had to clarify a prescription once, a physician is unlikely to make the same mistake again. But that need not be FDA's concern, so long as a medication error will not occur.

The Food and Drug Administration has approved applications for "Tylenol with Codeine" as the identical proprietary name of tablets, capsules, and an elixir. While Tylenol's core name does not imply tablets, the fact that the same name is used for all three dosage forms suggests that the FDA, in approving applications for those products, determined that the identifying descriptive information accompanying a prescription would be sufficient to distinguish one dosage form from the other. The use of "Elixir" as part of the proprietary name of the Whitby liquid product makes an even greater distinction between the tablet and liquid dosage forms than is done by the name, "Tylenol with Codeine."

Given the clarity of the proprietary name as a whole, we believe that the potential for confusion on the part of a prescribing physician or dispensing pharmacist as to whether a prescription calls for solid or liquid dosage form of Lortab® products is so remote as to be nonexistent.

Our position is reinforced by the fact that the Drug Enforcement Administration regulations in 21 C.F.R. Part 1306 governing the prescribing, dispensing and labeling of Schedule III controlled substances, including hydrocodone bitartrate in this formulation (21 C.F.R. § 1308.13(e)(4)), provide ample safeguards against the remote possibility of an imprecise or incomplete oral or written communication of the prescription from the practitioner to the pharmacist. For Schedule III drugs, however, that opportunity for confusion will, as a practical matter, rarely, if ever, arise. Section 1306.21 provides in pertinent part that:

> A pharmacist may dispense directly a controlled substance listed in Schedule III ... only pursuant to either a written prescription signed by the prescribing individual practitioner or an oral prescription promptly reduced to writing by the pharmacist.

21 C.F.R. § 1306.21 (emphasis added). The requirement of either written prescriptions or prompt reduction of oral prescriptions to writing by the pharmacist would, in our view, cause the pharmacist to recognize immediately any gaps or imprecision in the prescribing information and to secure the necessary information. A medication error would not occur.

Furthermore, § 1306.24(a) provides that the label of the dispensed drug must specify "directions for use and cautionary statements, if any ... as required by law." (emphasis added) Like the regulations set forth above, this provision obliges a pharmacist confronted with an imprecise or incomplete prescription to clarify or ascertain the intent of the prescribing practitioner. As a result, a medication error would not occur.

Nonetheless, to assure itself that the name "Lortab® Elixir" would not lead to prescribing or dispensing errors in hospital non-prescription situations, we consulted with Michael R. Cohen, assistant editor of Lippincott's Hospital Pharmacy magazine and editor of the Medication Error column. Mr. Cohen stated:

> I have also considered the oral liquid name which you propose, "Lortab Elixir." I can understand FDA's initial concerns. For aesthetic reasons, one would not ordinarily want to associate the syllable "tab" with an oral liquid. However, my own personal opinion is that it is a name extension of a product line and I do not feel this will be confusing or misleading to users since doses will need to be ordered by volume (ml, drams, teaspoonsful, etc.).

Because Mr. Cohen gave that opinion in January, 1988, I talked with him by telephone on March 10, 1992 to see whether any information had come to his attention since he wrote the letter that would change his mind. He said that he stood by his opinion and would be happy to talk with you about it.

3. A precedent has already been set.

Finally, regarding the Division's concern about setting a precedent for approving a product with a name that may suggest a different dosage form, two things must be said.

First, in light of everything stated above, I do not believe that FDA's approval of this name would be a *bad* precedent.

Second, such a precedent has been set many times over by the approval of USV Pharmaceuticals' Aquasol A (vitamin A) for a capsule (Armour Pharmaceuticals has an injection by the same name); Reid Rowell's "Aquatag" (benzthiazide) for a tablet; Wallace Labs' "Aquatensen" (methyclothiazide) for a tablet; Perrigo's "Cap-Profen" (ibuprofen) for a tablet as well as a capsule, and Forest Laboratories' "Elixophyllin" (theophylline), for capsules as well as a liquid dosage form. (All of these products are listed by proprietary name in APPROVED DRUG PRODUCTS, 10th Edition.)

Additionally, there are products that FDA has failed to take enforcement action against, such as Abbott Pharmaceuticals' use of "Vita-Kaps" for two different tablets; Armor Pharmaceutical's "Aquasol" not only for oral solutions but also capsules; Upjohn's "Unicaps" for both tablets and capsules; and Warner-Lambert's "Sinutabs" for both tablets and capsules.

Dr. Williams, we respectfully request that the Office of Generic Drugs withdraw its objection to the name, "Lortab® Elixir," and approve the application. If the Office is not prepared to withdraw the objection, we request a meeting with you and other appropriate officials. This is an issue of great importance to Whitby. The company hopes the matter can be resolved within the Office of Generic Drugs.

Sincerely yours,

Jess H. Stribling

Attachment

cc. Document Mail Center, Room 150
William Gottwald, M.D., President
Whitby Pharmaceuticals
Ms. Cerie McDonald
Mikart

ORIGINAL

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

FPL container 4 oz & 1 oz, P.I, labels & package insert satisfactory KS 3-23-92

March 9, 1992

NDA ORIG AMENDMENT AC FPL

Dr. Williams, M.D., Director
Division of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II (MPN II)
HFD 600
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
(5 mg/500 mg per 15 mL)
Major amendment to a pending application

Dear Dr. Williams:

Enclosed please find information submitted in support of a new batch of Hydrocodone Bitartrate and Acetaminophen Elixir (5 mg/500 mg per 15 mL) manufactured at the request of the Food and Drug Administration Atlanta District Office. The request by the Atlanta District Office was a result of the pre-approval inspection for this application.

Copies of the method validation and finished product and stabiliy testing procedures were included as part of a sample submission on January 27, 1992 and have therefore been omitted from this submission.

Thank you for your continued cooperation in the review of this application. Please feel free to contact us if you require any additional information.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald
Vice President

CBM/cc

Enclosure

RECEIVED

MAR 17 1992

GENERIC DRUGS

3-20-92

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

MIKART. INC.
PHARMACEUTICAL MANUFACTURERS

February 19, 1992

Mr. David Doleski
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
HFD-600
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Doleski:

As per your request, the following is a list of applications for which we are in the process of manufacturing new ANDA batches based on recommendations from the Atlanta District Office.

89-357	Hydrocodone Bitartrate and Acetaminophen Elixir (5 mg/500 mg per 15 mL)
81-051	Hydrocodone Bitartrate and Acetaminophen Elixir (7.5 mg/500 mg per 15 mL)
81-226	Hydrocodone Bitartrate and Acetaminophen Elixir (5 mg/500 mg per 15 mL)
89-450	Acetaminophen and Codeine Phosphate Elixir USP
81-118	Isoniazid Syrup USP
74-028	Amantadine Hydrochloride Syrup USP

We have submitted amendments to each of the listed applications with the intended dates for submission of information on the new batches.

Please feel free to contact us if you require any additional information.

Sincerely,

Cerie B. McDonald
Vice-President

CBM/ad

3/9/92

5.1

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

NA1
Partial response
to NA ltr 9/23/91
Review when response
is complete.
JM 2-11-92

NC Some of the response is in 4/14 ltr

NEW CORRESP

January 27, 1992

Dr. Roger Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg/15 mL
Sample submission

Dear Dr. Williams:

Mikart has submitted a sample of Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL to the Atlanta District Office of the Food and Drug Administration. Attached please find copies of the information submitted with the product sample to the district office. Included are copies of the batch record, method validation, and raw material results.

Thank you for your attention.

Sincerely,

Cerie B. McDonald
Vice-President

CBM/cc

RECEIVED
JAN 31 1992
GENERIC DRUGS

2-10-92

ORIGINAL

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

NEW CORRESP

January 22, 1992

Dr. Roger Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
(5 mg/15 mg per 15 mL)
Amendment to a pending appplication

Dear Dr. Williams:

Mikart has been requested to manufacture a new ANDA batch of Hydrocodone Bitartrate and Acetaminophen Elixir by the Atlanta District Office of the Food and Drug Administration. This request was made as a result of the pre-approval inspection for this application.

Mikart is currently in the process of manufacturing the new batch and conducting accelerated and room temperature stability. Information concerning the new batch, including the batch record and 90 day accelerated stability data, will be submitted as soon as it becomes available. We anticipate that this information will be ready for submission in February, 1992.

Thank you for your continued cooperation in the review of this application. Please feel free to contact us if you require any additional information.

Sincerely,

Cerie B. McDonald
Vice-President

RECEIVED
JAN 31 1992
GENERIC DRUGS

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-043

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

January 14, 1992

Dr. Roger Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
HFD-600
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP.

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg/15 mL
Amendment to a pending application.

Dear Dr. Williams:

As per Lucy Tang's telephone request enclosed please find a copy of the certificate of analysis and a copy of the method validation for the new batch of Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg/15 mL. Should you require any additional information do not hesitate to call.

Sincerely,

Cerie B. McDonald
Vice-President

CBM/cc

cc: Lucy Tang

ORIGINAL

RECEIVED
JAN 22 1992
GENERIC DRUGS

1-24-92

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

Called Mikart, talked to Cerie McDonald about this submission (dated Oct. 9, 1991). I told her that it is incomplete and cannot be reviewed. I also told her to submit the data ASAP. She said she was awaiting stability data to be collected. Also changing this to correspondence. 1/10/92 mpeckman

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

October 9, 1991

5.1

Dr. Williams, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFD-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

ORIG NEW CORRES

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg per 15 mL
Major amendment to an unapproved application

Dear Dr. Williams:

We have received your letter dated September 23, 1991 and we would like to respond to the issues raised. We have employed the outline of your letter to organize our response.

Please feel free to contact us if your require any additional information. Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald
Vice-President

CBM/ad

Enc.

ORIGINAL

RECEIVED
OCT 16 1991
GENERIC DRUGS

10/01/91

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

ANDA 89-557

Mikart, Inc.
Attention: Ms. Cerie B. McDonald
2090 Marietta Blvd., N.W.
Atlanta, GA 30318

SEP 23 1991

Dear Ms. McDonald:

Please refer to your abbreviated new drug application dated September 15, 1986, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir, 5 mg/500 mg per 15 mL.

Reference is also made to your communications dated February 12, 1991 and August 19, 1991.

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

1. It fails to provide adequate labeling information. In this regard:

   Insert: Satisfactory in draft

   However, before preparing final printed labeling please make the following minor editorial change:

   ADVERSE REACTIONS, Respiratory Depression

   Line 1- lower case "b" in bitartrate.

   Prepare and submit final printed insert labeling. We await the submission of final printed container labels.

2. We await your response concerning the proposed distributor proprietary name, Lortab Elixir.

3. We note you state the ——— container is not a marketed package size; however, you have submitted stability data for this package size. Please clarify.

4. We were informed on June 13, 1991 by the Investigations Branch at Atlanta District Office that a sample for the finished product for this ANDA was not collected. We understand you have committed to make a new batch to support this application using new equipment and new procedures.

5. You are to manufacture a batch of the drug product at least

— of the regular commercial production batch using the new equipment and new procedures. Please submit the executed batch record, finished product specifications and test data and 3-month accelerated stability data.

6. Please indicate your intended production batch sizes. Please submit blank batch records based on the new manufacturing procedures and equipment.

7. We acknowledge that ——————— and ——————— have been deleted as contract facilities from this application on your amendment dated August 19, 1991.

The file 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. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Michael G. Beatrice 9/19/91

Michael G. Beatrice
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Orig. ANDA 89-557
DUP/Division File
HFC-130 JAllen
HFD-638 K. Shah 9-18-91
HFD-637 FFang/LTang/9/10/91 9/18/91
HFD-82
HFD-637/PRickman/CSO 9/19/91
R/D initiated by FFang 9/19/91
Not Approvable - Major
LCT/9/10/91/89557N02.LLT
Disk # 8

ORIG

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

August 19, 1991

Dr. Roger L. Williams, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (MPN II)
HFD-600
5600 Fishers Lane
Rockville, MD 20857

OINC

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir (5 mg/500 mg per 15 mL)

Dear Dr. Williams:

In response to a June 19, 1991, letter from Carl Peck M.D. concerning designated facilities for Abbreviated New Drug Applications, we would like to update the list of designated facilities for this application. A list of designated facilities for all operations follows. This information replaces all previously submitted information concerning designated facilities. Any changes which have been made since the previously submitted information are noted below.

1. [redacted] has been deleted as an optional test facility for use in case of unforeseen circumstances.
2. [redacted] has been deleted as an optional test facility for use in case of unforeseen circumstances.
3. [redacted] a previously designated [redacted] for [redacted] has been acquired by [redacted]
4. [redacted] a previously designated [redacted] USP, has been acquired by [redacted]
5. [redacted] a previously designated [redacted] has been acquired by [redacted]
6. [redacted] a previously designated [redacted] for [redacted] has been acquired by [redacted]

Please feel free to contact us if you require any additional information.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald
Vice-President

CBM/ad
Enc.

RECEIVED
AUG 22 1991
GENERIC DRUGS

8/28/91

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

ORIG

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

NDA ORIG AMENDMENT

February 12, 1991

Dr. Williams, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFD-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg per 15 mL
Amendment to an unapproved application

Dear Dr. Williams:

We have received your letter dated February 4, 1991 and we would like to respond to the issues raised. We have employed the outline of you letter to organize our response. Many of the issues were previously addressed in our January 17, 1991 correspondence in response to a phone request from reviewer, Lucy Tang.

It is our understanding that all of the deficiencies with the exception of the proprietary name have been resolved by this letter. Thank you for your continued assistance in the review of this application.

Sincerely,

Cerie B. McDonald
Vice President

CBM/ad

Enc.

RECEIVED
FEB 2 1 1991
GENERIC DRUGS

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

FEB 4 [illegible]

ANDA 89-557

Mikart, Inc.
Attention: Ms. Cerie B. McDonald
2090 Marietta Blvd., N.W.
Atlanta, GA 30318

Dear Ms. McDonald:

Please refer to your abbreviated new drug application dated September 15, 1986, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL.

Reference is also made to your communications dated February 14, 1990 and August 24, 1990.

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

1. It fails to provide adequate labeling information. In this regard:

   I. General Comments

      A. We note that you have agreed to withdraw the proprietary name, Lortab Elixir. However, you have now indicated that you wish to retain the right for the name in question to be used by a distributor of this product. We do not find this acceptable. We are opposed to the use of this proprietary name by any firm for the reasons stated in our letters dated June 17, 1987 and July 21, 1988. We have contacted the Office of Compliance concerning the use of a proprietary name which has previously been deemed objectionable. We must again ask you to commit that this name will not be used by your firm or by any of your distributors for this product.

      B. We recognize your commitment that Russ Pharmaceuticals, Inc. will be the primary distributor for this product.

II. Container Labels- Satisfactory in draft for 30 mL, 4 fl oz, and 1 pint.

A. However, we encourage you to include an asterisk after hydrocodone in the established name as requested in item 1.II.B. in our letter dated December 19, 1989.

B. We note that you have not submitted a revised container label. Do you still intend to use this package size for repackaging as you originally indicated? We await your response.

III. Insert Labeling - Not Satisfactory

A. Warnings

Paragraph 3, line 2 - ...diagnosis or (rather than of) clinical...

B. HOW SUPPLIED

You have submitted a draft container label for a 30 mL package size yet this size does not appear in this section. Please comment. We cannot request final printed labeling until this issue is resolved.

Revise your package insert labeling, then prepare and submit final printed labels and draft insert labeling for our review and comment.

2. We acknowledge that the intended production batch of has been withdrawn from the application. The proposed production batch size has been changed from to

3. For the finished product:

a. the certificate of analysis of the finished product on page 41 of February 14, 1990 amendment is incomplete. The sources of the active ingredients, the product description and packaging lot # must be included.

b. Submit the certificates of analysis of the finished product for each of packaging lot (i.e., each of container/closure system).

4. For stability protocol:

   a. All future accelerated stability studies, the conditions are to be 40°C for this dosage form. For room temperature stability studies, actual temperature and humidity must be monitored and reported.

   b. All sizes of the container/closure system must be included in stability studies.

   c. Since you have agreed that a supplement will be submitted for rework processes, the general stability protocol for reworked batches submitted in the original application should be deleted.

5. For stability data:

   We note that the stability data for one oz was submitted in your amendment dated February 14, 1990. However, no information for the container/closure system was provided in the application. Please clarify.

6. Please be advised that samples of the active and inactive components, and the finished dasage form will be picked up by FDA district/laboratory staff. Since the drug product is not an article in the USP, all analytical methods will be validated.

7. We cannot locate your environmental impact statement from Mikart. The environmental impact analysis submitted on page 181 of original submission is from Russ Pharmaceutical, Inc. Please submit the current environmental impact analysis statement from Mikart, Inc.

The file 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. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Robert A. Jeanmi 2/24/91

Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 89-557
DUP
HFD-638 YMille 1/23/91
HFD-637FFang/LTang
Not Approvable - Major
LTang/89557N01.LLT/1-14-91

1/23/91 1/29/91

ORIG
4.1

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

January 17, 1991

Dr. Williams, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFD-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT
(AC)

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg per 15 mL
Amendment to an unapproved application

Dear Dr. Williams:

In response to a January 16, 1990 phone call from reviewer, Lucy Tang, enclosed please find the following requested information:

1. Labeling for the [redacted] package size which was inadvertently omitted from our 02-14-90 correspondence.

2. Revised stability protocol in which references to storage humidity and the section on reworked lots have been deleted.

Our 02-14-90 correspondence included labeling and stability information for the 1 fl oz (30 mL) package size. Since the 1 fl oz package size was withdrawn from this application in our 03-03-88 correspondence, this information is no longer relevant; therefore, please withdraw all references to the 1 fl oz package size from this application. We apologize for any confusion which may have resulted from our oversight.

It is our understanding that all of the deficiencies with the exception of the proprietary name have been resolved by this letter. Thank you for your continued assistance in the review of this application.

Sincerely,

Cerie B. McDonald
Vice President

CBM/ad
Enc.

cc. Desk copy to Lucy Tang

RECEIVED
JAN 18 1991
GENERIC DRUGS

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

ORIG

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

August 24, 1990

Mr. Richard Terselic, Acting Director
Division of Generic Drugs
Attention: Document Control Room
HFD-230, Room 17B-20
Food and Drug Administration
Center For Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg per 15 mL
Amendment to an unapproved application

Dear Mr. Terselic:

We would now like to respond to the only remaining issue in your correspondence dated December 19, 1989 concerning the above application.

We have employed the outline of the deficiency letter for our response, which can be found on the following pages.

There are no remaining deficiencies in this application and we request that approval be granted. Thank you for your prompt attention and review of this amendment.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald
Vice President
Mikart, Inc.

Enclosures

CBM/wlh

RECEIVED
AUG 30 1990
GENERIC DRUGS

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

February 14, 1990

NDA ORIG AMENDMENT

Mr. Richard Terselic, Acting Director
Division of Generic Drugs
Attention: Document Control Room
HFD-230, Room 17B-20
Food and Drug Administration
Center for Drug and Biologics
5600 Fishers Lane
Rockville, MD 20857

DRAFT LABELING

Re: ANDA 89-557 Hydrocodone Bitartrate and Acetaminophen Elixir
5 mg/500 mg per 15 mL
Amendment to an unapproved application

Dear Mr. Terselic:

We would like to acknowledge receipt on December 21, 1989, of your deficiency letter dated December 19, 1989 concerning the above application. Mikart, Inc. would now like to respond to most of the issues in your correspondence.

We have employed the outline of the deficiency letter for our response, which can be found on the following pages. Mikart will respond separately to item 4 concerning complete batch records and manufacturing process.

Thank you for your cooperation in the review of this amendment.

Sincerely,

Cerie B. McDonald
Vice President
Mikart, Inc.

Enclosures

CBM/wlh

RECEIVED
FEB 2 1 1990
GENERIC DRUGS

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510 FAX: 404-350-0432

DEC 19 1989

ANDA 89-557

Mikart, Inc.
Attention: Ms. B. McDonald
2090 Marietta Blvd., N.W.
Altanta, GA 30318

Dear Ms. McDonald:

Please refer to your abbreviated new drug application dated September 15, 1986, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL.

Reference is also made to your communications dated April 17, 1989 and August 28, 1989.

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

1. It fails to provide adequate labeling information. In this regard:

   I. General Comments

      A. We recognize your withdrawal of the proprietary name, Lortab Elixir, and consider it to be a commitment that this proprietary name will not be used by your firm or by any of your distributors for this product.

      B. In reviewing the application we were unable to find a statement from you indicating that Russ Pharmaceuticals, Inc. will be the sole distributor of this product. We do not, generally, review or approve distributor labels or labeling. However, if you commit to Russ Pharmaceuticals being the sole distributor, an exception can be made.

         We will provide comment on the labels and labeling since the comments apply without consideration for the distributor.

   II. Container Labels - Not Satisfactory

      A. Include a prominent expression of product strength directly beneath the established name.

         5 mg/500 mg per 15 mL

      B. We encourage the inclusion of an asterisk(*) after "Hydrocodone" in the established name and before the warning in the contents statement.

C. You indicated in your submission dated April 17, 1989 that the ——— package size is not a marketed package size but is intended for repackaging. Under the circumstances this package size should not be included in the insert labeling, however. if you should change your mind and decide to market ——— containers the HOW SUPPLIED section of the insert must be revised.

We would also like to remind you of the need to address all the issues raised in 21 CFR 201.122 and 21 CFR 201.150(a)(2).

~~(1) provide packaging and labeling supplements~~
~~(2) address all the issues raised in 21 CFR 201.150(a)(2).~~
~~prior to repackaging this product in an unapproved package size.~~

III. Package Insert - Not Satisfactory

A. DESCRIPTION

Penultimate Paragraph - The final word should be "which" (rather than ——).

B. CLINICAL PHARMACOLOGY

Paragraph 2, lines 3 and 4 - The numeral and unit of measurement should appear on the same line if at all possible.

C. PRECAUTIONS

1. Paragraph 2 - Line 4 should end in a semicolon(;) rather than a
2. Paragraph 8, line 8 - 0.7 (rather than ———

D. ADVERSE REACTIONS

Final Paragraph, sentence 1 - Delete ———————— ———.

E. DRUG ABUSE AND DEPENDENCE

Paragraph 1, line 2 - Subetances (plural)

IV. Revise your labels and labeling, then prepare and submit draft copy for our review and comment. We cannot request final printed labels or labeling until the issue discussed in item B under General Comments is resolved.

2. We acknowledge that Lortab Elixir has been withdrawn as the proprietary name for this product.

3. For components and composition:

   We note that the product name has been changed from Lortab Elixir to a generic name, Hydrocodone Bitartrate and Acetaminophen Elixir. Submit the revised components and composition statement of the drug product and/or your stability data report.

4. It fails to provide complete batch records and manufacturing process. In this regard:

   a) The equipment used for the executed batch of ——— (lot No K7372) is not fully described. It appears that it is different from that specified in the batch record for your intended production batch of ———

   b) It is noted the package sizes range from ——————— While you indicate ——— is a production batch, it must be a minimal size production batch.

   c) Based on the above considerations, please execute a batch based (use the same equipment) on the batch record for ——— The batch size should be at least ——————— Please submit executed batch record, finished product test specifications and data and 3-month accelerated stability data.

5. It fails to include complete stability data. In this regard:

   A. The sources of the active ingredients, batch size and manufacturing site must be included in the stability data report.

   B. Correct product name should be provided.

   C. Revise the stability data based on the above comments.

6. For finished Product:

   A. The certificates of analysis for the finished product on page 56 in your communication dated September 13, 1988 is incomplete. The following information should be included:

      (1) Please indicate batch size, the sources of active ingredients, manufacturing procedure (e.g., research, pilot or production batch) for each lot in the certificate of analysis.

(2) complete description of the drug product must be included.

(3) Provide correct product name.

B. Submit the revised certificate of analysis for the finished product based on the above comments.

C. The method validation for the finished product will be arranged upon the receipt of the revised certificate of analysis for the finished product.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Robert A. Jennifer 12/18/89

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc:
HFD-230 Y. Mille 12/14/89
HFD-237
YMille/FFang/LTang
bb/12-11-89
2734b/p. 1-4
NOT APPROVABLE 12/11/89

12/14/89

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

August 28, 1989

Mr. Richard Terselic, Acting Director
Division of Generic Drugs
HFD-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 Lortab Elixir
(Hydrocodone Bitartrate 5 mg/15 mL, Acetaminophen 500 mg/ 15 mL, Alcohol 7%)
Amendment to an unapproved application.

Dear Mr. Terselic:

Mikart would like to amend the above application to withdraw the proprietary name for this product, Lortab Elixir. The product name will be changed to a generic name, Hydrocodone Bitartrate and Acetaminophen Elixir. Enclosed is new labeling for the product which has been revised to include the generic name. No other changes have been made in the labeling. All future correspondence will refer to the product by the generic name.

There are now no remaining deficiencies in this application and we request that approval be granted. Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald,
Vice-President,
Mikart, Inc.

Enc.

CBM/ad

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

April 17, 1989

NDA ORIG AMENDMENT

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFD-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 for Lortab Elixir
(5 mg Hydrocodone Bitartrate, 500 mg Acetaminophen
and 7% Alcohol/15 mL)
Amendment to an unapproved application

Dear Dr. Seife:

We received your February 14, 1989 correspondence concerning the above application. We are responding to several parts of that letter. Further information will be forthcoming concerning the following points:

1.(1) A. & 1.(2) Proprietary Name issue

We will use the outline of your letter to organize our response.

Thank you for your cooperation in the review of this amendment.

Sincerely,

Cerie B. McDonald
Vice President
Mikart, Inc.

RECEIVED

Enclosures

CBM/wlh

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

February 22, 1989

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFD-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557, Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL)
Raw material sample submission

Dear Dr. Seife:

We submitted the raw material sample and other requested items on 02-22-89 to the Food and Drug Administration Drug Monitoring Branch in St. Louis as directed in your 02-14-89 correspondence.

We are including herewith a copy of the correspondence sent with the acetaminophen USP, [redacted] sample from [redacted]

Sincerely,

Cerie B. McDonald

Cerie B. McDonald
Vice President,
Mikart, Inc.

Enclosures

MAR 3 1989

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

ANDA 89-557

FEB 14 1989

Mikart, Inc.
Attention: Ms. Cerie B. McDonald
2090 Marietta Blvd. N.W.
Altanta, GA 30318

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL.

In order for our laboratory to ascertain that your bulk drug conforms to USP (if not USP, then appropriate) requirements, send the following materials to the address below:

Materials to be sent:

1. Acetaminophen USP [redacted] DMF # [redacted]
   Drug Substance

   [redacted]

2. A Certificate of Analysis (either yours or the [redacted] for the lot sent.

3. Standards - Reference, Impurity, and Internal - Send three times the amount required by the USP. [If you do not send the standard and St. Louis doesn't have it, the analysis will be delayed].

4. Copies of representative chromatograms and/or spectra (if applicable.)

5. Copy of the method of analysis if the drug substance is not compendial.

6. A Material Safety Data Sheet (OSHA Form 174) or equivalent information.

Address:

FDA/Division of Drug Analysis
Attention: Chief, Drug Monitoring Branch
1114 Market Street, Room 1002
St. Louis, MO 63101

These materials must be sent within 30 days of receipt of this letter. If you cannot send these materials by this date, please notify the Drug Monitoring Branch by letter. If you fail to send the requested materials, or properly notify the Drug Monitoring Branch Chief of any delay, this submission should be withdrawn. Send copies of all correspondence regarding the samples requested to the ANDA.

We recommend that you send the samples by registered mail/return receipt requested.

Sincerely yours,

Robert G. Johnson for 2-14-89

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFD-230
HFD-237
LTang 2/13/89
bb/2-8-89
1149D/Page 13-14
SAMPLE TO ST. LOUIS

ANDA 89-557

FEB 14 1989

Mikart, Inc.
Attention: Ms. Cerie B. McDonald
2090 Marietta Blvd. N.W.
Altanta, GA 30318

Dear Ms. McDonald:

We acknowledge receipt of your communication dated June 11, 1987, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL.

Reference is also made to your communication dated November 18, 1988.

Your letter details the Transfer of Ownership of ANDA, which provides for Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL) transfer from Russ Pharmaceuticals, Inc. to Mikart, Inc.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the approved application.

The material submitted is being retained as part of your application.

Sincerely yours,

Kenneth C. Johnson /for 2/14/89

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFD-230
HFD-237
LTang 2/13/89
bb/2-8-89
1149D/Page
TRANSFER OF OWNERSHIP

ANDA 89-557

FEB 14 1989

Mikart, Inc.
Attention: Ms. B. McDonald
2090 Marietta Blvd., N.W
Altanta, GA 30318

Dear Ms. McDonald:

Please refer to your abbreviated new drug application dated September 15, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL.

Reference is also made to your communications dated September 13, and 30, and November 18, 1988.

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

1. It fails to provide adequate labeling information. In this regard:

   (1) General Comment:

      A. We await your submission of another proprietary name for this product.

      B. Please explain the use of the ——— package size. Is it to be a marketed package size: If so, it should then be listed in the insert and container labels should be submitted. Is it intended for use as a bulk container? If so, why is it needed? It is our understanding that there are no longer any plans to package this product in unit dose cups.

   (2) Package Insert Labeling

      The text of the package insert labeling is satisfactory with the exception of items (1) A and B (above). We can not request final printed labels or labeling until these issues are resolved.

2. For components and composition:

   A. Alcohol should not be listed as an active ingredient in either your components and composition statement and/or your stability data report.

   B. Submit the revised components and composition statement of the drug product.

3. For Inactive ingredient:

   A. We await the quantitative compostion or components (ingredients) for the ——— when available.

4. For Active ingredients:

   A. Send samples (Acetaminophen USP, ———, to our St. Louis laboratory as requested by separate letter.

4. In regard to manufacturing process:

   a) Identify and describe each of the equipments used for batch lot No. K7372.

   b) Identify and provide test data for in-process controls.

   c) Describe the procedures taken for the protection of the drug product from light.

   d) Provide a production batch size (e.g., ———, for your stability data. This batch must be formulated with ——— that meet USP specifications.

5. For finished dosage form:

   A. On page 44 of your letter dated June 15, 1988, please state the source of the chromatogram submitted (reference standard/sample). Provide labeled chromatograms of representative alcohol standard and batch lot.

   B. We request your batch size for production and we request that all product validation be performed on batches produced on the scale for production.

6. Submit results of antimicfobial preservative - effectiveness for the product in 16 fl. oz and ——— market package when available.

7. It fails to provide adequate stability data. In this regard:

   A. Manufacture procedure (e.g. research, pilot or production batch) must be included in the stability data report.

   B. Alcohol USP should not be listed as an active ingredient.

   C. Submit the revised stability data including above comments.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Kent C. Johnson for 2-14-89

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

cc:
HFD-230 2/10/89
HFD-237
YMille/LTang 2/13/89
bb/2-7-89
1149D/Page 9-11
NOT APPROVABLE

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

November 18, 1988

Marvin Seife, M. D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 for Lortab Elixir
(Hydrocodone Bitartrate 5 mg/Acetaminophen 500 mg/15 mL alcohol 7 %)
Amendment to a pending application

Dear Dr. Seife,

In phone conversation of this date with the reviewer of this application, it was recommended that Mikart resubmit certain previously submitted letters regarding the transfer of ownership of this ANDA. Attached please find copies of the following:

1. Letter dated 6-11-87 from Russ Pharmaceuticals, Inc. to Dr. Seife transferring ANDA ownership to Mikart, Inc., effective 6-4-87.

2. Two letters dated 6-16-87 from Mikart, Inc. to Dr. Seife in which the ANDA transfer is stated to be effective 6-4-87, and which include Mikart's commitments to all previously made agreements within that ANDA.

May we please have your official acknowledgement of this ANDA ownership transfer.

Thank you for your cooperation.

Sincerely,

Cerie B. McDonald,
Vice-President,
Mikart, Inc.

Enc.
Desk copy to Dr. Lucia Tang

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

September 30, 1988

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 for Lortab Elixir (Hydrocodone Bitartrate 5 mg/Acetaminophen 500 mg/15 mL, alcohol 7%
Amendment to a pending application

Dear Dr. Seife:

We received your correspondence of 07-21-88 and we are responding to one of the two remaining issues left after our 09-13-88 response. Further information will be forthcoming on the following point:

1. proprietary name issue

Our response can be found on the following page. Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald,
Vice President,
Mikart, Inc.

Enc.

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

ANDA 89-557

Mikart, Inc.
Attention: Ms. Cerie B. McDonald
2090 Marietta Blvd. N.W.
Altanta, GA 30318

JUL 21 1988

Dear Ms. McDonald:

Please refer to your abbreviated new drug application dated September 15, 1986, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Elixir 5 mg/500 mg per 15 mL.

Reference is also made to your communications dated February 5, March 3, June 9 and June 21, 1988.

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

1. It fails to submit adequate labeling information. In this regard:

I. General Comments

We have considered your comments concerning the use of the root word Lortab, which includes "tab" as a part of the proprietary name for a liquid dosage form. We submitted your comments to the FDA Labeling and Nomenclature Committee and asked for their recommendations. They were in complete agreement with our initial comment that it is inappropriate to include "tab" as part of the name of a liquid preparation. Please suggest another name.

II. A. 1 Pint Container Labels - Not Satisfactory

See comment I.

B. Bulk Container Label - Not Satisfactory

See comment I.

III. Package Insert Labeling - Not Satisfactory

A. See comment I.

B. ADVERSE REACTIONS

Final Paragraph - Sentence 1 should read:

...the brain stem respiratory center.

C. OVERDOSAGE

Acetaminophen - Divide paragraph 2 into two paragraphs. The second paragraph begins with "Early symptoms."

IV. Revise your labels and labeling, then prepare and submit draft copy for our review and comment.

2. We acknowledge that the ——— package size has been withdrawn from application.

3. We will not review the draft of written agreement for bulk container since the ——— size has been withdrawn from applicaiton and none of the other size involve sending a ———

4. For active ingredients:

   A. Submit the revised and complete certificate of analysis for Acetaminophen, micronized from Mikart as previously requested in our letter dated November 4, 1987.

   B. In your tuture submission regarding specific gravity, we prefer that you follow the requirements and condition as outlined in USP XXI.

5. For componens and composition:

   A. Submit the components and composition statement of the drug product for the reformulation.

   B. The statement of components and composition in Master Manufacturing formula on page 56 are unacceptable. The composition of the active ingredients for the Lortab Elixir is stated as quantity (mg) per 15 mL. However, the composition of the excipients for the Lortab Elixir is stated as quantity (%). The unit should be consistent. Submit the revised Master formula as previously requested.

   C. Total weight per unit should also be included in the master formula card.

6. For inactive ingrediants:

   A. The information submitted regarding method and specification, and actual test results for FD&C Blue #1 color and D&C Yellow #10 color must be included. IR and UV spectra (sample and reference standard) should also be submitted.

   B. Submit the quantitative composition or components (ingredients) for the natural & artificial ——— as previously requested in our letter dated November 4, 1987.

   C. Submit IR spectra for infrared analysis on Natural and artifical ———

   D. Submit DMF number or reference from ——— as previously requested in our letter dated November 4, 1987.

7. It fails to submit complete master formula card, the details manufacturing and manufacturing process. In this regard:

   A. Revise the master formula card according to comments 5B and 5C.

   B. Identify and specify the equipment (e.g., _____) used in manufacturing procedures or instruction.

   C. Submit batch reconciliation with yield specifications.

   D. Rejection limits for accountability are not stated.

   E. Explain the difference between Lortab ___ Elixir and Lortab ___ Elixir. If these two products are not the same, specify the correct one in your next submission. Furthermore, in your master formula and batch record, the correct name of the drug product must be clearly specified (please see comments 11.).

   F. The number of random samples pulled from production line after filled is not stated.

   G. It fails to clarify the pH adjustment for the finished product during manufacturing process.

8. It fails to include in-process control testing protocol, which should include:

   A. Rework procedures are not described.

9. The test results for the preservative-effectiveness test from Lortab ___ Elixir is unacceptable. Submit the test results of preservative-effectiveness test for this drug product from _____ (see comments 12B).

10. For finished dosage form:

   A. Specify the method used for identification tests of active ingredients on the finished product specifications on page 142.

   B. Identification tests (e.g., IR) for active ingredients, Acetaminophen and Hydrocodone Bitartrate should be included in the finished product specifications.

   C. Submit the complete certificate of Analysis for the finished dosage product.

11. It fails to contain a satisfactory container/closure system. In this regard:

   A. We acknowledge that the containers manufactured by _____ have been withdrawn from the applicaiton.

   B. It fails to submit actual test results to demonstrate that _____ meets the current USP XXI requirements for containers as previously requested in our letter dated November 4, 1987.

C. We acknowledge that the [redacted] package and [redacted] package have been withdrawn from the application.

12. It fails to contain a satisfactory stability testing protocol and stability data. In this regard:

A. The stability protocol fails to include the test for antimicrobial preservative-effectiveness (USP XXI page 1151) as previously requested in our letter dated November 4, 1987.

B. It fails to provide results of antimicrobial preservative-effectiveness for the product in 4 fl. oz., 16 fl. oz. and [redacted] market package.

C. Mode of storage (e.g., liquid should be stored such that the drug product is in contact with the closure) should be indicated in the stability report. Stability studies and stability data under inverted challenge and room temperature conditions must also be included. Submit 1,2 and 3 month stability data under inverted or horizontal challenge conditions or 3,6,9,12 and 18 months room temperature stability data under inverted or horizontal conditions.

D. We cannot reach a conclusion regarding the propsoed 18 months expiration date until we are assured that the drug product is in contact with closure.

E. Manufacture procedure (e.g. research, pilot or production batch) must be included in the stability study studies.

F. Revise the stability protocol and the stability data according to above comments.

13. Samples for both the raw materials and the finished dosage product will be arranged upon the receipt of the revised and complete certificates of analysis.

The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

cc:
HFD-237 7/20/88 7/20/88
YMille/CChang/LTang/pw/7/18/88
1018D/not approvable

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research

for 7-21-88

for 7/20/88

Eric

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

June 21, 1988

AMENDMENT

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

RE: ANDA 89-557 Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Elixir, 5 mg/500 mg/15 mL, alcohol 7.0%)
Amendment to a pending application

Dear Dr. Seife:

Attached is the stability procedure SPG-002, Stability Indicating Method for the Assay of [redacted] in Acetaminophen-Containing Liquids. This procedure was inadvertently left out of our 6-15-88 response to part 1.C.(3) of your 11-04-87 letter. The procedure was referenced on page 001 of that response, but not actually included in the attachments.

A copy is attached for inclusion with the actual response. Three additional copies are attached for inclusion with the method validation package. As stated in our 6-15-88 letter, no more deficiencies remain in the application.

We apologize for the inconvenience. Thank you for your cooperation.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald,
Vice President
Mikart, Inc.

RECEIVED
JUN 28 1988
GENERIC DRUGS

cc: Dr. Lucy Tang

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

Orig

June 15, 1988

NDA ORIG AMENDMENT

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 for Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen, 5 mg/500 mg/15 mL with 7.0% alcohol)
Amendment to an unapproved application

Dear Dr. Seife:

We received your 11-04-87 correspondence concerning the above application. Previous responses were made on 2-5-88, 3-3-88 and on 6-9-88. We would now like to respond to all the remaining issues of that letter, using the outline of FDA's letter to organize our response.

This response contains the information which had been promised in our 6-9-88 correspondence as follows:

1.C.3. Method validation package for finished product/ stability methods on the revised formula.
3. Container/closure information
4. Stability data for the reformulated lot

Should you have any questions on this material, please feel free to call. There are now no deficiencies remaining in this application. Thank you for your cooperation in the review of this material.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald,
Vice-President
Mikart, Inc.

Enc.
cc: Desk copy to Dr. Lucy Tang,
Division of Generic Drugs

RECEIVED
JUN 17 1988
GENERIC DRUGS

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

Orig

June 9, 1988

NDA ORIG AMENDMENT

DRAFT LABELING

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 for Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen, 5 mg/500 mg/15 mL)
Amendment to an unapproved application

Dear Dr. Seife:

We received your 11-04-87 correspondence concerning the above application. On 2-5-88 and 3-3-88 responses concerning the proposed name and labeling revisions from your 06-17-87 letter mentioned in your 11-04-87 letter were completed. We would now like to respond to items 1 and 2 of that letter. We will use the outline of your letter to organize our response.

Mikart is hereby amending this application to withdraw the original formulation of this product. Mikart is also amending this application to add one additional packaging size, 4 fl oz. Packaging component information will be included in a separate response.

Additional information will be forthcoming concerning the following sections:

1.C.3. Method validation package for finished product/stability methods on the revised formula.
3 Container/closure information
4. Stability data for the reformulated lot

In addition to the requested information, Mikart is including a request for a waiver of in-vivo bioavailability studies on the reformulated product as part of section 1.C.3.

Concerning the list of communications included in the beginning of FDA's 11-04-88 correspondence, we note there is one error--no submissions concerning this application were made 09-24-87. Also, as mentioned above, after receiving your 11-04-87 letter, Mikart completed responses to your 06-17-87 letter in correspondence dated 02-05-88 and 03-03-88.

001

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

Should you have any questions on this material, please feel free to call. An additional response concerning the 11-4-87 deficiency letter will be made shortly.

Thank you for your cooperation in the review of this application.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald,
Vice President
Mikart, Inc.

enc.

cc: Lucy Tang--desk copy

MIKART, INC., 2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

Orig

March 3, 1988

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

DRAFT LABELING

Re: ANDA 89-557 for Lortab Elixir
(Hydrocodone Bitartrate 5 mg/15 mL,
Acetaminophen 500 mg/15 mL, Alcohol 7 %)
Amendement to an unapproved application

Dear Dr. Seife,

We have received your June 17, 1987 correspondence concerning the above application, and would like to respond in this letter to the labeling deficiencies raised in part 1. B - F. Our response to part 1. A. was included in our correspondence dated 02-05-88. Part 2 was previously answered.

Mikart is hereby withdrawing the package size of ——— which had been included in the original application. We therefore are not including the revised labeling for this package size.

We have employed the outline of the deficiency letter for our response, which can be found in the following pages. Please let us know if the text of the proposed labeling is acceptable.

Mikart is also preparing a response to your correspondence dated 11-04-87. The response will be forwarded to you under separate cover.

Sincerely,

Cerie B. McDonald,
Vice-President,
Mikart, Inc.

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MAR 7 1988
GENERIC DRUGS

Enc.

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

Orig

February 5, 1988

NDA ORIG AMENDMENT

Marvin Seife, M.D., Director
Division of Generic Drugs (HFN-230)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Room 17B-20
Rockville, MD 20857

Re: ANDA 89-557
LORTAB® ELIXIR (Hydrocodone Bitartrate 5 mg/15 mL
and Acetaminophen 500 mg/15 mL)

Dear Dr. Seife:

In your letter of December 23, 1986 regarding the above referenced ANDA, you requested that "Lortab® Liquid," the proprietary name of Russ Pharmaceuticals, Inc.'s ("Russ") hydrocodone bitartrate/acetaminophen liquid product, be altered on the ground that it may be misleading. In a January 30, 1987 amendment to its pending ANDA, Russ responded to your suggestion by agreeing to revise the name of the product to LORTAB® ELIXIR. At the same time, however, Russ requested reconsideration of the request that the other part of the proprietary name, Lortab®, be altered. Russ noted years of use of "Lortab®" to designate Russ' line of HCB/APAP products without any reported instances of confusion between liquid and solid dosage forms of Lortab® products.

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

In reply to Russ' request for reconsideration, comment 1.A. in your letter of June 17, 1987 concluded that the proprietary name "Lortab®" remained "undesirable ... [i]n summary ... because the core name implies tablets, yet the dosage form is not a tablet."

This letter amends the application by responding to the four points made in comment 1.A. The material below includes comment 1.A. from your June 17 letter.

> A. General Comment. We have considered your comments relating to LORTAB ELIXIR and have reviewed this matter with the Division of Drug Advertising and Labeling, and have the following remarks:
>
> > 1) You state that LORTAB is a trade name used to identify the line of products distributed by Russ Pharmaceuticals Incorporated. You do not make specific comment whether different drug entities are involved, or whether we are only talking about hydrocodone bitartrate and acetaminophen.

RESPONSE. All of the "Lortab®" products contain only hydrocodone bitartrate and acetaminophen. The Lortab® line consists of tablets containing 2.5 mg HCB/500 mg APAP, 5 mg HCB/500 mg APAP, 7.5 mg HCB/500 APAP, and the liquid product containing 5 mg HCB/15 mL/500 APAP/15 mL.

> > 2) Your justification on using LORTAB ELIXIR as a trade name is not compelling. While you state that

there have been no reports of problems associated with this proprietary name, we cannot evaluate this claim since we do not know the marketing history of LORTAB ELIXIR, or any other LORTAB product.

RESPONSE: Russ Pharmaceuticals has marketed approximately [redacted] tablets of the lower strength product since January 1980, [redacted] tablets of the 5 mg HCB product since November 1982, [redacted] tablets of the higher strength product since May 1981, and approximately [redacted] of the liquid product since February 1984. We repeat that there have been no reports of problems associated with this proprietary name.

3) Your claim that the prescribers of LORTAB products know the line well is immaterial. The Agency cannot be expected to evaluate educational efforts of a firm in explaining a misleading trade name. Further, the Agency believes precedent is an important feature of consistent decisions in this area of regulatory oversight. To permit the name you propose could be viewed as Agency agreement with this type of proprietary name.

4) In summary, we believe the proprietary name LORTAB ELIXIR is undesirable because the core name implies tablets, yet the dosage form is not a tablet.

RESPONSE: Section 502(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(a)) deems a drug misbranded if its labeling is false or misleading in any particular. We acknowledge that a misleading proprietary name may misbrand a product. We do

not concur, however, that the name, LORTAB® ELIXIR is misleading simply because the core name implies tablets, yet the dosage form is an elixir.

The full proprietary name of this product is LORTAB® ELIXIR, and the ELIXIR portion of the name, together with the identifying descriptive information accompanying a prescription, i.e., 16 fl. oz., makes perfectly clear that the product is a liquid and not a tablet.

We do not know of any evidence to support what we believe is a naive belief that prescribing physicians and/or pharmacists or other dispensers would look to one syllable of the first word of a product's two word proprietary name to discern its dosage form, especially when the second word in the proprietary name is the dosage form, "Elixir." Russ noted in its January 30, 1987 amendment instances in which a single proprietary name has been used to designate an entire line of related products in differing dosage forms. In the case of the Russ product line, the differing dosage form has a double proprietary name, LORTAB® ELIXIR, to distinguish the dosage from of the liquid product from the tablets.

Given the clarity of the proprietary name as a whole, we believe that the potential for confusion on the part of a prescribing physician or dispensing pharmacist as to whether a prescription calls for solid or liquid dosage form of Lortab® products is so remote as to be nonexistent.

Our position is reinforced by the fact that the Drug Enforcement Administration regulations in 21 C.F.R. Part 1306 governing the prescribing, dispensing and labeling of Schedule III controlled substances -- including hydrocodone bitartrate in this formulation (21 C.F.R. §1308.13(e)(4)) -- provide ample safeguards against the low probability of an imprecise or incomplete oral or written communication of the prescription from the practitioner to the pharmacist. For Schedule III drugs, however, that opportunity for confusion will, as a practical matter, rarely arise. Section 1306.21 provides in pertinent part that:

> A pharmacist may dispense directly a controlled substance listed in Schedule III ... only pursuant to either a written prescription signed by the prescribing individual practitioner or an oral prescription promptly reduced to writing by the pharmacist.

21 C.F.R. § 1306.21 (emphasis added). The requirement of either written prescriptions or prompt reduction of oral prescriptions to

writing by the pharmacist would, in our view, cause the pharmacist to recognize immediately any gaps or imprecision in the prescribing information and to secure the necessary information.

Furthermore, § 1306.24(a) provides that the label of the dispensed drug must specify "directions for use and cautionary statements, if any... as required by law." Like the regulations set forth above, this provision obliges a pharmacist confronted with an imprecise or incomplete prescription to clarify or ascertain the intent of the prescribing practitioner. As a result, there would be very little chance that inaccurate dispensing would occur due to confusion regarding a practitioner's intent to prescribe LORTAB® ELIXIR or one of Russ' Lortab® tablets.

We recognize that there are hospital situations in which a physician may order a floor nurse to dispense a drug for immediate administration to a bed patient. Such an order is not a "prescription" under DEA regulations (21 C.F.R. 1306.02(f)) that would be controlled by the prescription writing requirements cited above. However, the physician would use the name of the product, LORTAB® ELIXIR and the identifying descriptive information, e.g., 2 teaspoonsful.

Nonetheless, to assure itself that the name LORTAB ELIXIR® would not lead to prescribing or dispensing errors in hospital non-prescription situations, because Russ is as concerned as FDA to prevent misinterpretations by nurses as well as pharmacists, Russ consulted with Michael R. Cohen, assistant editor of Lippincott's Hospital Pharmacy, and editor of the Medication Error columns. Mr. Cohen stated:

> I have also considered the oral liquid name which you propose, "Lortab Elixir." I can understand FDA's initial concerns. For aesthetic reasons, one would not ordinarily want to associate the syllable "tab" with an oral liquid. However, my own personal opinion is that it is a name extension of a product line and I do not feel this will be confusing or misleading to users since doses will need to be ordered by volume (ml, drams, teaspoonsful, etc.).

A copy of Mr. Cohen's letter is attached.

On these grounds, we renew the request for approval of the name of this liquid product, LORTAB® ELIXIR.

Sincerely yours,

Cerie B. McDonald

Cerie McDonald

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

file

November 10, 1987

Marvin Seife, M.D., Director
Division of Generic Drugs
Attention: Document Control Room
HFN-230, Room 17B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 89-557 for Lortab Elixir (Hydrocodone Bitartrate 5 mg/15 mL and Acetaminophen 500 mg/15 mL)
Amendment to a pending application

Dear Dr. Seife,

We received your November 4, 1987 communication. This is to notify you that in accordance with 21 CFR part 314.120, Mikart, Inc. will amend this application. Details will be forthcoming in separate correspondence.

Sincerely,

Cerie B. McDonald,
Vice-President,
Mikart, Inc.

RECEIVED
NOV 16 1987
GENERIC DRUGS

Enc: Form 356h

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

ANDA 89-557

Mikart, Inc.
Attention: Ms. Cerie B. McDonald
2090 Marietta Blvd. N.W.
Atlanta, GA 30318

NOV 4 1987

Dear Ms. McDonald

Please refer to your abbreviated new drug application dated September 15, 1986 submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Lortab Elixir (Hydrocodone Bitartrate 5 mg/15 mL and Acetaminophen 500 mg /15 mL).

Reference is also made to your correspondence dated January 30, June 11, June 16, July 1, and September 4, 1987.

Reference is also made to our letter dated June 17, 1987.

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

1. It fails to assure that the drug dosage form and components will comply with the specifications and tests described in an offical compendium, if such article is recognized therein, or if not listed, or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality and purity. In this regard:

   A. For active ingredients:

      (1) The certificate of analysis for Acetaminophen from [redacted] is incomplete. Several specifications (limits) and tests results (analysis) merely state "Passes Test". The specifications (limits) and test results (analysis) should be either a numerical value or a descriptive statement. Submit IR and UV spectra for identification tests from [redacted] Submit the revised certificate of analysis for Acetaminophen from [redacted]

      (2) The certificate of analysis for Acetaminophen USP, [redacted] from applicant is imcomplete. The specifications and tests results on page 135 should be either a numerical value or descriptive statement. Complete USP monograph testing should be performed. [redacted] should be included in the certificate of analysis for Acetaminophen. Please submit the revised certificate of analysis from applicant.

      (3) DMF# [redacted] will be reviewed at a later time.

      (4) In the absence of DMF number for alcohol [redacted] Complete information as to the manufacture and control of active ingredient (alcohol) must be included in the applicant.

(5) Submit the certificate of analysis for ___ alcohol from ___.

(6) The certificate of analysis for ___ alcohol (on page 172) is incomplete and unacceptable. The specifications should be either a numerical value or a descriptive statement. The specifications for specific gravity must be compliance with USPXXI. Submit the revised cerificate of analysis for ethyl alcohol from applicant.

(7) The certificate of analysis for Hydrocodone Bitartrate from ___ on pages 7 & 165 is unacceptable. The lot number, date analysis, tests method, specifications, and actual test results must be included. Submit the revised certificate of analysis for Hydrocodone Bitartrate from manufacturer.

(8) Submit IR and UV spectra for Hydrocodone Bitartrate from manufacturer.

(9) The raw material for Hydrocodone Bitartrate is USP grade not USP ___ Please comment and clarify.

B. For ___ manufacturing product (Hydrocodone Bitartrate USP ___ mixture):

(1) The Hydrocodone Bitartrate USP ___ was stated in the components and composition section and the Master manufacturing formula. The Hydrocodone Bitartrate in DMF ___ is pure and USP graded ___ Please provide DMF number for Hydrocodone Bitartrate ___ mixture. Submit the components and compostition of hydrocodone bitartrate ___ mixture. Submit the certificate of analysis for hydrocodone bitartrate ___ mixture from applicant and manufacturer.

C. For components and composition:

(1) The statement of components and composition on pages 13 and 18 are unacceptable. The composition of the active ingredients for the Lortab Elixir is stated as quantity (mg) per 15 mL. However, the composition of the excipients for the Lortab Elixir is stated as quantity (%) per TSP. The unit should be consistent. Please clarify and submit the revised components and composition statement of the drug product.

(2) Total weight per unit should also be included in the components and composition section. Clarify the grade for the Hydrocodone Bitartrate ___ mixture.

(3) The Hydrocodone Bitartrate DMF # ___ is pure and USP ___. It contains ___ assay of Hydrocodone Bitartrate calculated on the ___ Hydrocodone Bitartrate USP ___ equivalent to Hydrocodone Bitartrate USP) is stated in the components and composition section on page 17. Please comment, clarify and reformulate.

D. For inactive ingredients:

(1) The certificate of analysis for [redacted] is incomplete. [redacted] assay and identification tests A and B should be included. Submit the revised COA from [redacted]. Submit specifications and tests results for [redacted] from applicant.

(2) The certificate of analysis for [redacted] is incomplete. Actual tests results for identification. [redacted] should be included. Submit the revised COA from [redacted] Submit specification and test results for readily [redacted] from applicant.

(3) No information on [redacted] was submitted. Please submit compositional information or DMF reference from [redacted] Submit a copy of monograph of [redacted] Submit certificate of GRAS status.

(4) Submit IR spectra of identification test for [redacted]

(5) Submit IR spectra of identification test for [redacted]

(6) Submit IR spectra of identification test for [redacted] The certificate of analysis for [redacted] is incomplete. [redacted] range should be included. Submit the specification and test results for [redacted] range from applicant or manufacturer.

(7) Submit IR spectra of identification test for [redacted]

(8) Submit the certificates of analysis for [redacted], and their FDA color certificates.

(9) Submit method and specification and actual test results for [redacted] from applicant.

(10) No information on Natural and Artificial [redacted] was submitted. Please submit:

a) The [redacted] of the flavor.
b) Compositional information (or DMF reference from the [redacted])
c) certificate of GRAS status.

2. We will not review formulation, manufacture, processing, finished dosage form and stability data until you clarify the use of Hydrocodone Bitartrate [redacted] mixture or the contents of Hydrocodone Bitartrate per unit and the statement of components and composition of the drug product.

3. It fails to contain a satisfactory container/closure system. In this regard:

   A. It fails to submit actual test results to demonstrate that ——— meets the current USP requirements for containers. Please indicate type ——— used in ——— Please submit the actual test results of the ——— manufactured by

   B. The test results submitted on page 96 from ——— is unacceptable. Please submit actual test results to demonstrate that 16 oz. HDPE bottles manufactured by ——— meets the current USP XXI requirements.

   C. It fails to submit actual test results to demonstrate that ——— meets the current USPXXI requirements for containers.

   D. It fails to submit actual test results to demonstrate that ——— meets the current USPXXI requirements.

   E. For Unit dose package:

      (1) It fails to submit actual test results of light transmission test, physico-chemical test and permeation test to meet current USP XXI requirements for unit dose container.

      (2) It fails to submit actual test results that ——— meets the current USPXXI requirements for container.

      (3) It fails to submit physical description (size, shape, engineering diagrams of unit dose container/closure system).

      (4) Identify the person who performs a part of operation of unit dose package and bulk package.

4. It fails to contain a satisfactory stability testing protocol. In this regard:

   A. Assay for the degradation product ——— tested at 30, 60 and 90 days under 37°C and 75% relative humidity must be included in the stability program.

   B. The following information should also be included. Stability Commitment: A signed statement that any lots which may fall out of specification will be promptly withdrawn from the market.

   C. Formulation (quantitative composition) should be included in the stability summary form.

D. [redacted]

E. [redacted]

F. [redacted]

G. [redacted]

H. Submit the revised stability protocol.

5. It fails to provide adequate labeling. See comment 1 in our letter dated June 17, 1987.

The file is now closed. You are required to take one of the actions, described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substanial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Kenneth C. Johnson /for 11-4-87

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc: 11/3/87
CChang/LTang/
kl/1118b
11/3/87

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

Orig

September 4, 1987

Marvin Seife, M.D., Director
Division of Generic Drugs
HFN-230, Room 17-B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

ORIG NEW CORRES

Re: ANDA 89-557 for Lortab Elixir

Dear Dr. Seife,

In accordance with Section 314.420 of 21 CFR Subpart F, we are hereby notifying all persons to whom DMF "authorization to reference" letters have been issued that Mikart has submitted an annual update of its Type I DMF #4913. Sections of DMF # — were incorporated by reference in Mikart's Type II DMF # — concerning the above ANDA.

The changes submitted do not detract from any information previously submitted and do not adversely affect this ANDA.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald,
Vice-President
Mikart, Inc.

RECEIVED
SEP 11 1987

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

Orig

July 1, 1987

Marvin Seife, M.D., Director
Division of Generic Drugs
HFN-230, Room 17-B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

Re: ANDA 89-557 for Lortab Elixir (Hydrocodone Bitartrate 5 mg/ Acetaminophen 500 mg/15mL, Alcohol 7.0%)
Amendment to an unapproved application

Dear Dr. Seife,

In your December 23, 1986 correspondence, you had requested that all manufacturing, testing, processing and packaging information contained in Mikart's Drug Master Files # — and # — be included in this ANDA. An initial response to this request had been made on January 30, 1987. This amendment serves as a further response to that request.

All relevant information from Mikart's Type II DMF # — is included herewith in the form of an amendment to this application. The pages have been labeled in the upper right corner with the ANDA section to which they belong. Since Mikart's Type I DMF # — contains only general information concerning Mikart's operation, facility and personnel, this information has not been repeated herewith.

In addition, a revised methods validation for this product is included herewith. Also attached are three unbound copies of this item.

Mikart has also received the June 17, 1987 letter of deficiency concerning this application. A response to that letter will be forthcoming shortly.

RECEIVED
JUL 15 1987
GENERIC DRUGS

Sincerely,

Cerie B. McDonald

Cerie B. McDonald,
Vice-President,
Mikart, Inc.

Enclosures

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

ANDA 89-557

JUN 17 1987

Russ Pharmaceuticals, Inc.
Attention: Mr. Russ Maddox
P.O. Box 20507
Birmingham, Alabama 35216

Dear Mr. Maddox:

Please refer to your abbreviated new drug application dated September 15, 1986, submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Lortab Liquid (Hydrocodone Bitartrate 5 mg/15 mL and Acetaminophen 500 mg/15 mL).

Reference is also made to your correspondence dated January 30, 1987.

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

1. It fails to provide satisfactory unit dose, carton, bulk package and container labels and package insert labeling. Please revise in accord with the recommendations below, then prepare and submit draft copies for our review and comment.

   A. General Comment

   We have considered your comments relating to LORTAB ELIXIR and have reviewed this matter with the Division of Drug Advertising and Labeling, and have the following remarks:

   1) You state that LORTAB is a trade name used to identify the line of products distributed by Russ Pharmaceuticals Incorporated. You do not make specific comment whether different drug entities are involved, or whether we are only talking about hydrocodone bitartrate and acetaminophen.

   2) Your justification on using LORTAB ELIXIR as a trade name is not compelling. While you state that there have been no reports of problems associated with this proprietary name, we cannot evaluate this claim since we do not know the marketing history of LORTAB ELIXIR, or any other LORTAB product.

   3) Your claim that the prescribers of LORTAB products know the line well is immaterial. The Agency cannot be expected to evaluate educational efforts of a firm in explaining a misleading trade name. Further, the Agency believes precedent is an important feature of consistent decisions in this area of regulatory oversight. To permit the name you propose could be viewed as Agency agreement with this type of proprietary name.

   4. In summary, we believe the proprietary name LORTAB ELIXIR is undesirable because the core name implies tablets, yet the dosage form is not a tablet.

B. Unit Dose Labels - Not Satisfactory

See the General Comment concerning the proprietary name.

C. Carton Labels - Not Satisfactory

1. Usual Dosage - adult (spelling)

2. See the General Comment concerning the proprietary name.

3. See comment 2 under Package Insert Labeling.

D. Container Label - Not Satisfactory

1. See the General Comment concerning the proprietary name.

2. See comment 2 under Package Insert Labeling.

E. Bulk Container Labels

1. The firm should supply evidence of a proposed "written agreement" which will address all the issues raised in 21 CFR 201.150(a)(2). We are especially interested in the plan for transfer of labels and labeling to the repacker.

2. We do not believe the sentence following the Federal CAUTION statement should appear on the label. This should instead be a part of the above cited written agreement.

3. The approximate volume in milliliters should be noted on the label.

4. The storage recommendations for the bulk container may well be more restrictive than the marketed package labels. We also suggest that conditions of relative humidity be noted.

5. See the General Comment concerning the proprietary name.

6. Supplement 5 to the USP-NF requires that a whole number should be shown without a decimal point that is followed by a terminal zero. [e.g. 4 mg (rather than ~~4.0~~) and 500 mg (rather than ~~500.~~).

F. Package Insert Labeling - Not Satisfactory

1. TITLE:

See the General Comment concerning the proprietary name.

2. DOSAGE AND ADMINISTRATION

The second paragraph should be revised to read:
The usual adult dosage is one or two tablespoonfuls every four to six hours as needed for pain. The total 24 hour dose should not exceed 8 tablespoonfuls.

3. HOW SUPPLIED:

   a. The recommendations to the pharmacist on the type of container to use for dispensing should appear in a section that is separate from the storage recommendations.

   b. Include an expression of product strength based on 15 mL.

2. It fails to contain adequate formulation, manufacturing, testing, processing, and packaging information. In this regard, please be advised that the review of this ANDA is being deferred until complete information is included in the application. Drug Master Files are not regulated documents and cannot be referenced by an ANDA for information pertaining to formulation, manufacturing, testing, processing and packaging. The Code of Federal Regulations requires that this information be contained in the regulated document (Abbreviated New Drug Application). Please submit this information as part of ANDA 89-557. If you have additional questions regarding the information required to complete this application, please contact Mr. David Rosen of our Review Support Branch (301) 443-0193.

The file is now closed. You are required to take one of the actions described under 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Robert L. Johnson /for 6-12-87

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237 Y. Mille 6/16/87 CC 6/16/87
YMille/CChang/WMarnane/tr/6/12/87
0008D
Not Approvable cej 6/16/87

0R16

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

June 16, 1987

Change in ownership on 4/22/92 BSolow

Marvin Seife, M.D., Director
Division of Generic Drugs
HFN-230, Room 17-B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

ORIG NEW CORRES

RE: Change in ownership of ANDA 89-557, Lortab Elixir (5 mg Hydrocodone Bitartrate USP, 500 mg Acetaminophen USP per 15 mL)

Dear Dr. Seife:

This letter serves to inform the Division of Generic Drugs that the ownership of the above-mentioned ANDA has been transferred from Russ Pharmaceuticals, Inc., to Mikart, Inc., effective June 4, 1987.

It is our understanding from conversations with David Rosen that the transfer of a pending application can be handled without interrupting the review process currently underway. We appreciate any special consideration you might give this transfer as we are anxious to cooperate in every way possible with your department for the expeditious approval of this ANDA.

Mikart, Inc. is committed to all agreements, promises, and conditions made by the former owner as contained in the application and the amendments to date.

Mikart, Inc. has obtained a complete copy of the pending application, including amendments and other FDA correspondence. A completed form FDA 356h is attached.

Thank you for your cooperation with this matter.

Sincerely,

Cerie B. McDonald

Cerie. B. McDonald
Vice President
Mikart, Inc.

Enclosure

RECEIVED

JUN 19 1987

GENERIC DRUGS

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510

MIKART, INC.
PHARMACEUTICAL MANUFACTURERS

June 16, 1987

Marvin Seife, M.D., Director
Division of Generic Drugs
HFN-230, Room 17-B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

RE: Change in ownership of ANDA 89-557, Lortab Elixir (5 mg Hydrocodone Bitartrate USP, 500 mg Acetaminophen USP per 15 mL)

Dear Dr. Seife:

Mikart, Incorporated hereby agrees to advise the FDA of any change in the processing, controls, or marketing of the above referenced ANDA as required in 21 CFR Part 314.70 following approval of the application.

Supplements to the approved application will be submitted for those changes requiring the same. Other information will be included in the annual report as required.

Thank you for your cooperation in this matter.

Sincerely,

Cerie B. McDonald

Cerie B. McDonald
Vice President
Mikart, Inc.

Drug

Russ Pharmaceuticals Inc.

June 11, 1987

DRUG ANDA BOOKS

Dr. Marvin Seife
Director
Food and Drug Administration
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
Rockville, MD 20857

Dear Dr. Seife:

This letter is to inform you that all rights to the pending ANDA application on our product LORTAB LIQUID, ANDA 89-557 has been transferred to Mikart, Inc. in Atlanta, Georgia. The effective date of transfer was June 4, 1987.

If you have any questions, please do not hesitate to contact us.

Sincerely,

RUSS PHARMACEUTICALS, INC.

Russell H. Maddox
President

RECEIVED
JUN 17 1987
GENERIC DRUGS

RHM/bkl

cc: Mikart, Inc.
Jess Stribling

Post Office Box 20507 • Birmingham, Alabama 35216 • Phone (205) 822-2730

[redacted]

Orig

Russ Pharmaceuticals Inc.

January 30, 1987

Marvin Seife, M.D., Director
Division of Generic Drugs
HFN-230, Room 17-B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

DRAFT LABELING

Re: ANDA 89-557
Lortab Liquid (Hydrocodone Bitartrate 5 mg/15 mL and Acetaminophen 500 mg/15 mL)

Dear Dr. Seife:

We received your October 15, 1986 and December 23, 1986 letters concerning the above ANDA. In these communications, additional information and certain changes were requested. We would like to respond herewith to those requests, using the format of the letters.

Regarding Point 1 of the October 15, 1986 letter, Mikart's DMF has been assigned number 6584.

For Point 2, a CGMP certification statement is attached.

Concerning item 3, the requested environmental impact assessment has also been attached.

For item 4, our contract [redacted] has provided additional information concerning their facilities, personnel, and controls. Details can be found on the following pages.

In your communication of December 23, 1986, various labeling changes and questions related to our reference of Mikart's Drug Master Files were mentioned. On the following pages are the details of our response.

There are now no deficiencies remaining concerning this application. Please let us know if you need further information or clarification.

Sincerely,

RUSS PHARMACEUTICALS, INC.

Russell H. Maddox
President

RECEIVED
FEB 3 1987
GENERIC DRUGS

Post Office Box 20507 • Birmingham, Alabama 35216 • Phone (205) 822-2730

ANDA 89-557

DEC 23 1986

Russ Pharmaceuticals, Inc.
Attention: Mr. Russ Maddox
P.O. Box 20507
Birmingham, Alabama 35216

Dear Mr. Maddox:

Please refer to your abbreviated new drug application dated September 15, 1986, submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Lortab Liquid (Hydrocodone Bitartrate 5 mg/15 mL and Acetaminophen 500 mg/15 mL).

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

1. It fails to provide satisfactory unit dose, carton, bulk package and container labels and package insert labeling. Please revise in accord with the recommendations below, then prepare and submit draft copies for our review and comment.

A. General Comments:

1. [redacted] to [redacted]

2. Also of concern is the reference to tablet dosage form in the proprietary name for a liquid product. [Lortab]

We believe this name is inappropriate, as a general principle, for the reason cited directly above. Also, we believe that confusion will likely occur from prescriptions and hospital orders when the description is not precise, as is often the case. Carried further, the results of this name can be predicted to require needless confirmation communications between physician, nurse, and pharmacist; and also result in medication errors.

Please submit another proprietary name for our consideration.

B. Unit Dose: Not Satisfactory

1. We agree that the USP requires that the amount of active drug be labeled in terms of each 5 mL portion of the liquid. However, as a practical matter, we will allow this _____ to express the amount of drug in terms of the total content since it is a _____ container.

therefore we suggest:

Each 15 mL contains:
etc.

2. You may delete the, _____ statement to conserve space.

3. The NDC should appear above the proprietary name, not beneath it.

4. _____

C. Carton: Not Satisfactory

1. See comment 1 under _____.

2. While the expression of strength is required to be stated in terms of active drug per 5 mL, we recognize the reasonableness and need to show the content per 15 mL (as 15 mL is the usual adult dose). Therefore, we propose that following simple table appear on labels and labeling which will reflect both expressions:

	Per 5 mL	Per 15 mL
Hydrocodone Bitartrate (WARNING: May be habit forming)	1.67 mg	5 mg
Acetaminophen	167 mg	500 mg
Alcohol	7%	7%

(Note: Delete the word "_____" which appears after alcohol)

3. The symbol for degrees (°) is a superscript not a subscript.

4. We prefer _____ container (rather than _____

D. Container: Not Satisfactory

1. Container Label

a. See comment 1 under Unit Dose

b. See comments 2 and 3 under Carton

2. Bulk Container Label

a. Delete [redacted]

b. Please add the storage recommendations.

E. Insert: Not Satisfactory

1. DESCRIPTION

See comment 1 under [redacted]

2. OVERDOSAGE

a. Hydrocodone, Treatment, Paragraph 1, Line 7 should read:

...naloxone hydrochloride....

b. Acetaminophen, Signs and Symptoms, Paragraph 1, Line 3- overdose (rather than overdosage)

3. HOW SUPPLIED

Storage Recommendations-The symbol for degrees (°) is a superscript not a [redacted]

2. It fails to contain adequate manufacturing, testing, processing and packaging information. In this regard, please be advised that the review of this ANDA is being deferred until complete information is included in the application. Reference to Mikart (Type I DMF, copy enclosed with application, and Type II DMF [redacted]) is not acceptable. All information except proprietary information regarding the synthesis of the active ingredients must be contained within the approved application. Please submit this information as part of ANDA 89-557.

The file is now closed. You are required to take one of the actions described at 21 CFR 314.120 which will either amend or withdraw the application, or if you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Kent Johnson (FOR

12-23-86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc:
HFN-237
YMille/CChang/WMarnane/tr/12/16/86
1202S/pg 5-7
Not Approvable

12/22/86
cap/12-22-86

NOV 18 1986

NDA 89-557

Russ Pharmaceuticals, Inc.
Attention: Russ Maddox
P.O. Box 20507
Birmingham, Alabama 35216

Dear Sir:

Reference is made to your request for waiver of in-vivo bioavailability requirements you submitted onSeptember 15, 1986 for Hydrocodone Bitartrate/Acetaminophen Syrup, 5 mg/500 mg per 15 ml.

Your request has been reviewed by our Division of Bioequivalence and they have the following comments:

"The Division of Bioequivalence agrees that the information submitted by Russ Pharmaceuticals, Inc. demonstrates that Hydrocodone Bitartrates/Acetaminophen 5 mg/500 mg per 15 ml syrup falls under 21 CFR Section 320.22 (b)(5) and the Waiver Policy of the Division of Bioequivalence (May 5, 1986) of the Bioequivalence Regulations. The waiver of in vivo bioequivalence study requirements for the combination syrup product, 5 mg/500 mg per 15 ml, is granted. From the bioequivalence point of view, the firm has met the in vivo bioequivalence requirements. Accordingly, an in vivo bioequivalence study does not need to be undertaken."

Sincerely yours,

Marvin Seife 11/1

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc: HFN-230
Marnane
MSeife/JSturm/jt/11-14-86
BIO 051Rb

NDA 89-557

OCT 15 1986

Russ Pharmaceuticals Inc.
Attention: Mr. Russ Maddox
P.O. Box 20507
Birmingham, Alabama 35216

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 for the following:

NAME OF DRUG: Lortab Liquid (Hydrocodone Bitartrate 5 mg/15 mL and Acetaminophen 500 mg/15 mL)

DATE OF APPLICATION: September 15, 1986

DATE OF RECEIPT: September 19, 1986

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

Please submit the following:

(1) The number for the Mikart DMF as soon as it is available;

(2) CGMP certification from Russ Pharmaceuticals;

(3) Environment Impact Assessment from Russ Pharmaceuticals;

(4) Complete description of the facilities, personnel and controls employed by Unit Dose Laboratories, an Environmental Impact Assessment, and CGMP statement.

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

Sincerely yours,

10-14-86

Ken E. Johnson for 10-15-86

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

cc: HFN-230 DUP
Chang/jt/10-6-86
Ack 0323b

89-557

RUSS®

Russ Pharmaceuticals Inc.

September 15, 1986

Marvin Seife, M.D., Director
Division of Generic Drugs
HFN-230, Room 17-B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Seife:

Enclosed please find two copies of an Abbreviated New Drug Application for Lortab Liquid. Also included herewith is a desk copy of the manufacturer's Type II Drug Master File, which was previously submitted to the FDA.

Thank you for your cooperation in the review of this application.

Sincerely,

RUSS PHARMACEUTICALS, INC.

Russ Maddox
President

RM/bkl

Enclosure

3 Copies of the Analytical Methodology is also on file in the Doc. Rm

Pls Note DMF Desk Copy is on file in the Doc. Room

RECEIVED
SEP 19 1986
GENERIC DRUGS

Post Office Box 20507 • Birmingham, Alabama 35216 • Phone (205) 822-2730

MIKART, INC.

PHARMACEUTICAL MANUFACTURERS

September 2, 1986

Marvin Seife, M.D., Director
Division of Generic Drugs
HFN-230, Room 17-B-20
Food and Drug Administration
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, MD 20857

Re: Abbreviated New Drug Application for Lortab Liquid

Dear Dr. Seife:

Aside from the components of this application, please find three unbound sets of all methodologies pertinent to this application for raw material, finished product and stability analyses. These methodologies have been attached confidentially by the manufacturer, Mikart, Inc.

Mikart has also confidentially included herewith 1 copy of the related Type II Drug Master File with cover letter dated August 20, 1986, for the convenience of the reviewer. This DMF contains manufacturing, packaging and labeling information concerning the drug. Originals were previously submitted to the FDA. References are made within the ANDA to the "accompanying Type II Drug Master File with cover letter dated August 20, 1986."

Sincerely,

Cerie B. McDonald

Cerie B. McDonald,
Vice-President,
Mikart, Inc.

2090 MARIETTA BOULEVARD, N.W., ATLANTA, GEORGIA 30318 PHONE: 404-351-4510