CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-021/S-001

Name: Efidac/24 (Pseudoephedrine HCl) Extended Release Tablets, 240 mg

Sponsor: ALZA Corporation

Approval Date: February 1, 1993

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-021/S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-021/S-001

APPROVAL LETTER

FEB 1 1993

NDA 20-021/S-001

Alza Corporation
P.O. Box 10950
950 Page Mill Road
Palo Alto, CA 94303-0802

Attention: Janne Wissel
Director, Regulatory Affairs

Gentlemen:

Please refer to your supplemental new drug application dated January 8, 1993, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Efidac/24 (Pseudoephedrine HCl) Extended Release Tablets.

The supplemental application provides for an alternate facility to carton the drug product. The facility is located in the Vacaville facility of Alza at 771 Eubanks Drive.

We have completed our review of the supplemental application and it is approved. We remind you that you must comply with the requirements set forth under 27 CFR 314.80 and 314.81 for approved new drugs.

Sincerely yours,

Guirag Poochikian, Ph.D.
Supervisory Chemist
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CC:
NDA 20-021/S-001
HFD-150/Division File
HFD-150/GKPoochikian
HFD-150/MCTheodorakis MCTheodorakis 1/29/93.
HFD-150/CSchumaker
R/D init by GPoochikian 1/27/93
F/T by Lenci S. 1/29/93\ ap 1/29/93
DOC.\ALZA\20021-01.SLA

APPROVAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-021/S-001

CHEMISTRY REVIEW(S)

JAN 27 1993

CHEMIST'S REVIEW	Organization	NDA Number
	FDA/ HFD-150	20-021

Name and Address of Applicant:
Alza Corporation
950 Page Mill Road, P.O. Box 10950
Palo Alto, CA 94303-0802
tel.: 415-494-5059
Attention: Dr. Janne Wissel

AF Number

Supplement Number S-001 **Date** 1/8/93

Name of Drug	Nonproprietary Name
Efidac/24 Extended Release Tablets	Pseudoephedrine HCl Extended Release Tablets

Amendment & dates

Supplement Provides for
an alternate facility to carton the drug product. The facility is located in the Vacaville facility of Alza at 771 Eubanks Drive.

Related INDs, NDAs and DMF

Pharmacological Category	How Dispensed
	Rx | OTC x

Dosage Form:	Potency:
Extended Release Tablets	240 mg/tablet

Chemical Name and Structure

Records & Reports Current yes no

Reviewed yes no

COMMENTS:
See page 2.

CONCLUSIONS and RECOMMENDATIONS:
It is recommended that approval be granted for this supplemental application.

CC:
NDA 20-021
HFD-150/Division File
HFD-150/MTheodorakis
HFD-150/GPoochikian
HFD-150/CSO
R/D Init. by: GP 1/27/93
F/T by:MCT/_____
DOC.\ALZA\20021-01.SUP

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Michael C. Theodorakis Ph.D.	MTheodorakis	1/26/93

Distribution: Original Jacket Reviewer Division File

12. RELATED INDs, NDAs, DMFs:

17. COMMENTS:

a. Currently the manufacturing including blistering (primary container) and cartoning (secondary container) of the drug product is performed at 700 Eubanks Drive. The Applicant has requested to move only the cartoning operation to an adjacent facility at 771 Eubanks Drive.

b. This facility has been previously approved for Ocusert Pilo 20 (Pilocarpine) Ocular Therapeutic System (NDA 17-431) and Ocusert Pilo 40 (Pilocarpine) Ocular Therapeutic System (NDA 17-548). The approval to these supplemental applications was granted on 12/11/92.

c. The EER report issued for Ocusert Pilo 20 (Pilocarpine) Ocular Therapeutic System (NDA 17-431) and Ocusert Pilo 40 (Pilocarpine) Ocular Therapeutic System (NDA 17-548) indicate that the facility at 771 Eubanks Drive was found to be acceptable. See attached EER.

Attachment:
EER completed 11/24/92

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration

11-5-92 3868

MEMORANDUM

Center for Drug Evaluation and Research

DATE: November 4, 1992

NOV 9 1992

TO: Division of Manufacturing & Product Quality (HFN-320)

FROM: Division of Medical Imaging, Surgical and Dental Drug Products

HFD-160

REQUESTER'S NAME: Marilyn Apfel

PHONE: 443-1560

ESTABLISHMENT EVALUATION REQUEST

Sterile Product: XXXXX **Non Sterile Product:**

Application and Supplement No. NDA 17-431/SCM-027

Brand Name (if any): OCUSERT Pilo-40 Ocular Therapeutic System (and Pilo-2)

Establishment Name, Dosage Form and Strength: pilocarpine; topical; 11 mg/system and 5 mg/system

Profile Class Code: NEC

Priority Classification: (See SMG BD-4820.3)

Applicant's Name: ALZA Corporation

Address: ~~P.O. Box 10950~~, 950 Page Mill Road, Palo Alto, CA 94303-0802

Facilities to be Evaluated:(Name, full Address, DMF No., and responsibility)

For HFN-320 Use
Status & Date of Inspection:

1. ALZA Corporation
   771 Eubanks Drive
   Vacaville, CA
   (new cartoning site)

   AC- 8/26/91

2.

3.

4.

Other Information or Special Requests:

For HFD-320 Use Only:

Date Received: 11/12/92

CGMP Compliance Status of Facilities Evaluated: Acceptable

CSO: M. Thompson

Date Completed: 11/24/92

Distribution: Original and First Copy: HFN-320
Remaining Copies: Requesting Office Use

3274(6/86)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-021/S-001

CORRESPONDENCE

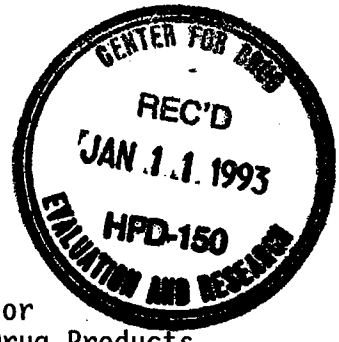
alza

NDA NO. 20021 REF. NO. 001

NDA SUPPL FOR SCM

NDA 20-021
Volume 19.1

January 8, 1993



Center for Drug Evaluation and Research
Office of Drug Evaluation I, HFD-150
Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

Attention: Gregory P. Burke, M.D., Ph.D., Director
Division of Oncologic and Pulmonary Drug Products

Subject: EFIDAC/24® pseudoephedrine hydrochloride (240 mg):
Supplemental New Drug Application

Dear Dr. Burke:

In accordance with 21 CFR 314.70 (b)(2)(iv) we are submitting a supplemental new drug application to use an alternate facility to carton the drug product. Attached is the rationale for moving the cartoning operation, a description of the new facility, and an environmental assessment.

Currently, the product has been approved to be cartoned in an approved facility in Vacaville, California. Due to a demand for space at the current facility, a new facility adjacent to the current building has been identified. Only the cartoning operation will be moved to the adjacent building. The new facility will be operated in the same manner, under the same procedures as the current facility, and will be supervised and directed by the same staff.

Similar supplements for moving the cartoning operation have been filed and approved. These include Ocusert® Pilo-20 (pilocarpine) Ocular Therapeutic System (NDA 17,431), Ocusert® Pilo-40 (pilocarpine) Ocular Therapeutic System (NDA 17,548), Progestasert® Intrauterine Progesterone Contraceptive System (NDA 17,553), Catapres-TTS® (clonidine) Transdermal Therapeutic System (NDA 18,891), and Nicoderm® (nicotine transdermal system) (NDA 20,165).

If you have any questions regarding this information, please feel free to contact me at (415) 494-5059 or via facsimile at (415) 494-5050.

Sincerely,

Janne Wissel
Director
Regulatory Affairs

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

1/8/1993 ALZA LETTER

alza

ENVIRONMENTAL ASSESSMENT

ADDITIONAL CARTONING SITE

PRODUCT: EFFIDAC/24®

1. **DATE:** December 24, 1992

2. **NAME OF APPLICANT:** ALZA Corporation

3. **ADDRESSES:**

(corporate)	ALZA Corporation 950 Page Mill Road P.O. Box 10950 Palo Alto, CA 94303-0802
(cartoning, current)	ALZA Corporation 700 Eubanks Drive Vacaville, CA 95688-9470
(cartoning, new)	ALZA Corporation 771 Eubanks Drive Vacaville, CA 95688-9470

4. **DESCRIPTION OF PROPOSED ACTION:**

A. Description of the Requested Approval

The proposed action is FDA approval of an additional site/building for the cartoning of EFFIDAC/24®. This building is located at 771 Eubanks Drive in Vacaville, California, adjacent to the current packaging facility for this product.

B. Need for the Proposed Action

The approval is needed so product demand can be accommodated in a timely manner to ensure availability of this medication, indicated for the treatment of nasal decongestion, to the public. The current packaging site located at 700 Eubanks Drive in Vacaville, California, does not have sufficient capacity to meet the increasing demand for packaging of all commercial products.

C. Location Where Product will be Produced

The product will be cartoned by ALZA Corporation in their Vacaville, California facility at 771 Eubanks Drive. The site is adjacent to the approved packaging facility for EFFIDAC/24 at 700 Eubanks Drive. It is located in the Vaca Valley Industrial Park, a short distance east of Vacaville. The park

ALZA CORPORATION, 950 PAGE MILL ROAD, P.O. BOX 10950, PALO ALTO, CA 94303-0802 (415) 494-5000 TELEX 345526

is zoned Industrial and, at present, is partially developed with light industrial and manufacturing uses. Site improvements (building and land) must receive approval from a local Community Development Department. Adjacent to the site is grazing land, currently planned for subdivision into one-quarter and one-third acre residential parcels.

The type of environment present at these locations, specific to the vicinity of product manufacturing, is described in the following sections.

Location - ALZA Corporation's Vacaville facilities are located on two parcels in the city of Vacaville. The 15-acre site at 700 Eubanks Drive is currently approved for all processes associated with the manufacture of EFFIDAC/24. The adjacent 7-acre site at 771 Eubanks Drive will be used for product cartoning only. These facilities are approximately 30 miles west of Sacramento and 75 miles northeast of San Francisco. Coordinates for the plant's location are latitude N 38°24′ and longitude W 121°58′. The city of Vacaville's population was estimated to be 66,100 people in 1990. Sacramento, the closest large city, had a population of 1,336,500 people in 1987.

Weather/Air Resources - Annual rainfall for Vacaville is 24.5 inches. The mean summer temperatures range from a high of 91°F to a low of 54°F, while mean winter temperatures range from a high of 59°F to a low of 38°F. The Vacaville area is designated non-attainment for ozone, and for 10-micron particulate matter. The area is currently in attainment with primary standards for sulfur oxides, nitrogen dioxides, and carbon monoxide. Vacaville has incorporated into its regulations the California Air Quality Standards, the National Emission Standards for Hazardous Air Pollutants (NSHAPS), the District Solvent Emission Regulations, and the New Source Rule. There are no Class I Visibility Areas within 30 miles of the plant. Prevailing winds in the plant's vicinity are from the north.

Water Resources - Process water from the 700 Eubanks Drive site is collected and pumped with a grinder pump to a sanitary well where it mixes with effluent from the sanitary sewers and is discharged into the city of Vacaville's waste water treatment facilities. Storm water drainage flows directly into the Putah South Canal, which is adjacent to the northwest lot line of the plant, and into another small creek which runs through the property less than 300 feet to the south of the manufacturing building. Putah South Canal also supplies water to towns downstream of the facility. There are currently three groundwater monitoring wells on the plant property, and approximately six private wells located within one-quarter mile of the site. The 771 Eubanks Drive site has sanitary sewer discharge only and there are no groundwater monitoring wells.

According to the Flood Boundary and Floodway Map prepared by FEMA in August 1982, these sites are in Zone X, indicating an area for a 500-year flood, or an area covered by less than one foot of water in a 100-year flood zone. The facilities derive all of their potable water from the city of Vacaville.

Land Resources - The terrain surrounding the plant is valley flatland with low hills to the west. Elevation at the site is approximately 120 feet above sea level. Geological data indicate that the plant sits upon Quaternary and Tertiary alluvium, consisting primarily of unconsolidated to poorly consolidated, irregularly interstratified silty to sandy clay deposits with some sand and gravel lenses. Underlying the alluvial sedimentary deposits are approximately 2,500 feet of non-marine, moderately consolidated deposits of clay, silt, silty fine sand, gravel, and volcanoclastic materials of the Tehama Formation. Consolidated bedrock below the Tehama Formation is believed to consist of sandstone and shale of the Great Valley Sequence. No faults are known to pass through the site, although the active Green Valley Fault is located thirteen miles to the west.

D. Location Where Product will be Used

The finished product is intended for use by consumers throughout the United States and in other countries where approved for sale.

5. IDENTIFICATION OF DRUG SUBSTANCE:

Drug substance is Pseudoephedrine Hydrochloride

Nomenclature: *α-[1-(Methylamino)ethyl]benzenemethanol hydrochloride*

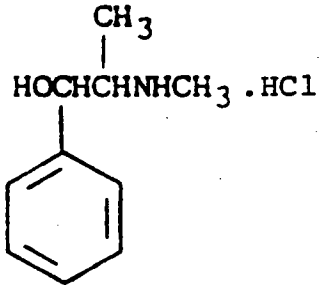
CAS Registration Number: 345-78-8

Molecular Weight: 201.7

Appearance: White or off-white crystals

Empirical Formula: $C_{10}H_{15}NO \cdot HCl$

Structural Formula:



6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

i. Liquid Waste Streams - In the process of cartoning EFFIDAC/24, no aqueous waste streams will be generated. Small quantities of organic solvent (isopropanol) used for equipment cleaning and wipedown are transferred to a permitted waste staging facility where they are placed in disposal containers by trained hazardous waste technicians and held for removal by a licensed waste hauler to an EPA permitted incinerator. No other liquid waste streams are generated in the course of product cartoning. The storage and disposal of liquid waste at the Vacaville plants is subject to, and in compliance with, the Federal Clean Air Act, Federal Resource Conservation and Recovery Act (40 CFR Part 262, Generators of Hazardous Waste; Part 263, Transporters of Hazardous Waste; Part 268, Land Disposal Restrictions), State of California Hazardous Waste Control Law (California Health and Safety Code, Division 20, Chapter 6.5, Hazardous Waste Control; Chapter 6.7, Underground Storage of Hazardous Substances), Title 22 of the California Code of Regulations (Chapter 30, Minimum Standards), Central Valley Regional Water Quality Control Board, City of Vacaville Municipal Code (Chapter 13.08, Sewer Use Ordinance), and Solano County Hazardous Materials Management Ordinance.

ii. Air Emissions - Trace quantities of organic solvents used for cleaning will be emitted into the air, in accordance with local environmental regulations. Air emissions at the Vacaville plants are subject to, and in compliance with, the Federal Clean Air Act, and regional regulations established by the Yolo-Solano Air Pollution Control District (Regulations I-VII, excepting VI, which regulates agricultural burning).

iii. Solid Waste - All EFFIDAC/24 waste generated in the cartoning operations is transferred to a permitted waste staging facility as described in 6.i. above. ALZA is registered with the EPA as a waste generator (EPA No. CAD 982475964). Drug product waste is placed in disposal containers and held for removal by a licensed waste hauler to an EPA permitted incinerator. Non-hazardous items (spent air filters, waste paper from packaging, labeling, and cartoning) will be drummed for disposal in approved landfills or by incineration, as necessary. Handling and disposal of solid waste streams at the Vacaville plant is subject to, and in compliance with, the Federal Resource Conservation and Recovery Act (RCRA), State of California Hazardous Waste Control Law, and Solano County Hazardous Materials Management Ordinance. Specific citations are the same as those in Section 6.i.

iv. Employee Protection - The action proposed herein is approval of an additional site for cartoning, which precludes personnel contact with the active product, i.e. systems are already sealed in pouches and/or blister packs when received at the

cartoning operation. The entire EFFIDAC/24 manufacturing process is carried out under the supervision of qualified personnel, with training provided for normal and emergency operations. ALZA employees who work with the dosage form receive training in general safety and chemical handling techniques. ALZA has a computerized Material Safety Data Sheet (MSDS) system which provides employees immediate access to chemical safety information. Employees also receive training in the specific hazards of each chemical with which they work. Spill control protection is provided in all areas where chemicals are handled. Employee protective clothing, such as gloves, coveralls or lab coats, safety shoes, and protective equipment such as safety glasses, are used during the manufacturing process to assure compliance with the Occupational Safety and Health Act (OSHA) of 1971, CAL-OSHA, and the Hazards Communication Act of 1985. Air, liquid, and solid waste emissions will comply with the environmental control regulations cited in the preceding sections. The plants are in compliance with all applicable OSHA requirements.

v. Environmental Exposure - Quantities of substances that enter environmental media (i.e. soil, air, or water) as a result of the cartoning process are inconsequential. Cartoning operations will utilize filters with an efficiency greater than 95 percent for air discharged to the environment. Spent dust filters that have been exposed to the drug product will be handled as hazardous waste and drummed for offsite disposal at an EPA permitted incinerator.

vi. Consumer Use and Disposal - Use of EFFIDAC/24 results in introduction of the package and carton components to the environment. Disposal is expected to be by conventional means, i.e. incineration or landfill.

vii. Disposal of Returns - Information on the manner in which returned systems are disposed of is provided in Attachment 1.

7. FATE OF EMITTED SUBSTANCES IN ENVIRONMENT:

Because this supplement is specific to an additional cartoning site for EFFIDAC/24, no drug product will be released to the environment. Packaging and cartoning materials will be disposed of as described in Section 6.v.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

Trace amounts of solvent will be emitted into the air, in accordance with applicable environmental regulations. The solvent will be at negligible concentration in the air stream. Landfilling of the non-hazardous components such as paper will not release significant quantities of harmful compounds into the ground.

9. **USE OF RESOURCES AND ENERGY CONSUMPTION:**

There will be minimal depletion of natural resources used to package and dispose of components of this system. Energy will be used in the operation of the equipment.

There will be no effect on any endangered species.

There will be no effect on any property listed in the National Register of Historic Places.

10. **MITIGATION MEASURES:**

The handling measures outlined herein have been implemented as a measure to mitigate the effects of this production process on the environment. No further measures are required. The entire cartoning operation will be carried out under the supervision of qualified personnel, with training provided for normal and emergency operations.

11. **ALTERNATIVES TO THE PROPOSED ACTION:**

The alternative to the proposed action is to disapprove the use of the additional cartoning facility for the product and prevent this product from meeting market demand.

12. **LIST OF PREPARERS:**

Douglas S. Burhyte, Director, Corporate Process Engineering, ALZA

13. **CERTIFICATION:**

To Whom It May Concern:

The undersigned official of ALZA Corporation hereby certifies that the information contained in the accompanying Environmental Assessment specific to the cartoning of EFFIDAC/24® at the ALZA facility in Vacaville, California, is true, accurate, and complete to the best knowledge of the firm or party responsible for its preparation.

(Name) PIETER P. BONSEN

SR. VICE PRESIDENT
(Title)

DECEMBER 24, 1992
(Date)

ATTACHMENT 1 - DISPOSAL of RETURNS

Drug product damaged in the distribution network or designated as a customer return is returned either to ALZA Corporation or CIBA-Geigy. These materials are then processed within established procedures and, like all potential wastes, are subject to company waste management guidelines. All materials are reviewed according to a disposition hierarchy: elimination, reduction, followed by reuse or recycle before a material is deemed a waste. Once a material is deemed a waste, treatment (incineration, neutralization, biological) to render a material less hazardous is preferred, followed by landfill. All materials, whether of value or waste, are managed in accordance with all site environmental permits and licenses and in accordance with all applicable Federal, State, and Local regulations. The operations necessary to manage this drug product are no different than those currently existing at these sites and are not expected to generate any new or unusual compliance problems. If disposal is required, incineration is the preferred treatment method to assure complete destruction (99.9%) with disposal of residual ash via secure landfill.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date January 11,1993

NDA No. 20021

ALZA Corporation
950 Page Mill Road
Palo Alto, CA 94304

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: EFIDAC/24

NDA Number: 20021

Supplement Number: S-001

Date of Supplement: January 8, 1993

Date of Receipt: January 11, 1993

All communications concerning this NDA should be addressed as follows:

National Center for Drugs and Biologics(HFN-150)
Attention: Document Control Room 17B-28
5600 Fishers Lane
Rockville, MD 20857

Nancy L. Crase

FOR: Supervisory Consumer Safety Officer
Division of Oncology and Radiopharmaceutical
Drug Products
National Center for Drugs and Biologics

FORM FDA 3217e (6/83)

☆ GPO : 1983 O - 408-424