CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-803

ENVIRONMENTAL ASSESSMENT and/or FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

LOTEMAX™
(Loteprednol Etabonate)
0.2% Ophthalmic Suspension
NDA 20-803

Pharmos Corporation

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
(HFD-550)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-803

Lotemax™

(Loteprednol Etabonate)

0.2% Ophthalmic Suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Lotemax™, PHARMOS Corporation has prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(b)(3)*, which evaluates the potential environmental impact of the manufacture, use and disposal of the product.

Loteprednol Etabonate is a chemically synthesized drug which is administered as a sterile ophthalmic suspension in treatment of the signs and symptoms of seasonal allergic conjunctivitis of the eye. The drug substance is made at SIPSY, Avrille', France and the drug product is manufactured by Bausch & Lomb, Tampa, Florida. The finished drug product will be used mainly by patients in their homes.

Loteprednol Etabonate may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Drug product that expires, or is returned from the field will be separated from the packaging and disposed of as a non-hazardous substance at a licenced facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal

quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

4/24/97
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

4/24/97
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)

FREEDOM OF INFORMATION ACT

NDA 20-803

THE INFORMATION CONTAINED IN

NDA SECTION 3.2.11

CHEMISTRY, MANUFACTURING & CONTROLS
DRUG PRODUCT
ENVIRONMENTAL ASSESSMENT
VOLUME 10

MAY BE MADE AVAILABLE TO THE PUBLIC

LEXICON

THE DRUG SUBSTANCE

LOTEPREDNOL ETABONATE
LE

THE DRUG PRODUCT

LOTEPREDNOL ETABONATE 0.2% OPHTHALMIC SUSPENSION
LOTEMAX™ ALLERGY
LOTEMAX™ ANTI-ALLERGY
LEA
LE 0.2%
CORE 353

OTHER LOTERPREDNOL ETABONATE PRODUCT (NDA 20-583)

LOTEPREDNOL ETABONATE 0.5% OPHTHALMIC SUSPENSION
LE
LE 0.5%
LOTEMAX™
CORE 299

MANUFACTURER

BAUSCH & LOMB PHARMACEUTICALS, INC.
BLP
B&L

3.2. Drug Product

3.2.11. Environmental Assessment

Note to the Reviewer:

This Environmental Assessment may be made available to the public under the Freedom of Information Act.

Environmental Assessment Report

Loteprednol Etabonate 0.2% Ophthalmic Suspension

1. **Date** December 1996

2. **Name of Applicant** PHARMOS Corporation

3. **Address** 2 Innovation Drive
Alachua, Florida 32615
Tel: 904 452-1210
Fax: 904 462-5401

4. **Description of the Proposed Action**

a. The Proposed Requested Approval

Pharmos Corporation is submitting a New Drug Application (NDA) for approval of loteprednol etabonate 0.2% ophthalmic suspension (LE 0.2%).

b. Need for the Action

LE 0.2% is a topical product which will be used in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. Annually, an estimated 2.3 million Americans use prescription medications to treat this condition. Loteprednol etabonate (LE) is derived from prednisolone and posseses a potency similar to dexamethasone but causes fewer side effects than other corticosteroids in the treatment of intraocular inflammation. LE is presumed to act at the glucocorticoid (Type II) receptors.

c. Locations Where the Product Will Be Produced

The drug substance will be manufactured by

SIPSY
Route De Beaucouzé - B.P. 79
49242 Avrillé Cedex
France
Tel: 33-41-43-32-11
Fax: 33-41-42-75-55

The drug product will be manufactured by

Bausch & Lomb Pharmaceuticals, Inc.
5800 Hidden River Parkway
Tampa FL 33637
Tel: 813 975-7700
Fax: 813 975-7757

d. Locations Where the Product Will Be Used and Disposed Of

Once approved, LE 0.2% will be used by individuals throughout the United States, primarily on an out-patient basis. Disposal of unused product by the consumer will be through municipal and private household trash collection.

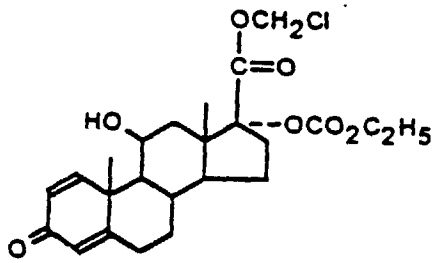
Bausch & Lomb will be responsible for returned and rejected goods. The product will be taken out of any outer packaging which, along with the package insert, will be recycled separately. The plastic containers will be emptied, shredded, rinsed, and recycled. The liquid contents will be collected and disposed of as a non-hazardous substance. (See Item 6 b for additional information on disposal.)

Bausch & Lomb is located in an urban area having a flat terrain and a subtropical climate.

5. Identification of Chemical Substances That Are Subject to the Proposed Action

a. Drug Substance Identification

Common Name: loteprednol etabonate

Chemical Names:	Androsta-1,4-diene-7-carboxylic acid, 17-[(ethoxycarbonoy1)oxy]-11-hydroxy-3-oxo-, chloromethyl ester, (11ß, 17α)- Chloromethyl 17-ethoxycarbonyloxy-11ß-hydroxy-3-oxo-androstra-1,4-diene-17ß-carboxylate
CAS Number:	82034-46-6
Molecular Weight:	466.96
Molecular Formula:	$C_{24}H_{31}O_7Cl$
Structural Formula:	

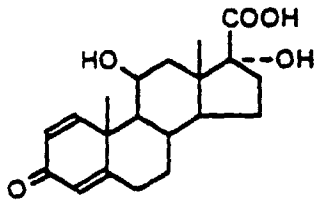
Loteprednol Etabonate

b. Drug Substance Physical Description

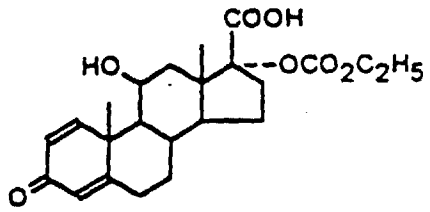
Appearance:	White crystalline powder
Melting Point:	232 ± 2°C
Vapor Pressure:	Not determined
pH:	Not applicable; Loteprednol Etabonate has no ionizable groups
Solubility:	DMSO: 34.05% DMF, 31.75% Ethanol: 0.8365% Propylene Glycol: 0.2241% Water: 0.0008%, or 8 µg L^{-1}
Partitioning:	3.04 (log $K_{acetonitrile/water}$) (Ref.: Alberth *et al.*, 1991)
Additives:	None. (Benzalkonium chloride is present as a preservative.)

c. Drug Substance Impurities

As supplied, loteprednol etabonate has no significant amounts of impurities (≤ 2%). In the proposed drug product, the chief impurities are Δ_1 cortienic acid etabonate (PJ-91) and Δ_1 cortienic acid (PJ-90) (sum of the two ≤ 0.05% w/v). Both impurities are closely related to LE and may arise from any of the following: synthesis (drug substance), hydrolysis (drug product), or metabolism (in humans).



PJ-90 (Pharmos)



PJ-91 (Pharmos)

d. Excipients

The excipients used in LE 0.2% are common USP/NF pharmaceutical ingredients: glycerin, povidone, tyloxapol, edetate disodium dihydrate, benzalkonium chloride, purified water, and sodium hydroxide or hydrochloric acid (as pH adjusters).

6. Introduction of Substances into the Environment

a. Drug Substance Manufacturing - SIPSY (France)

Emissions of loteprednol etabonate will controlled by SIPSY in such a way as to ensure compliance with all local emissions requirements (see appendix). This includes the disposal of unused rejected drug substance.

b. Drug Product Manufacturing - Bausch & Lomb (Tampa FL)

In the production facility, adequate ventilation during raw material handling and product compounding wil be provided to maintain dust and vapor levels below the TLV, STEL, and PEL values for the ingredients. Personal protective equipment (e.g., NIOSH-approved respirators, goggles or safety glasses, gloves, and protective clothing) will be used. The minimal amounts of materials emitted into the air will be trapped in HEPA filters. Spills will be collected and containerized for disposal. Total annual solid waste quantities will be less than 2.5 kg, assuming an annual usage rate of 50 kg of loteprednol etabonate drug substance and a 5% loss (waste) rate.
Both solid and liquid wastes from the production of LE 0.2% will be disposed of as non-hazardous waste by a licensed facility. Bausch & Lomb currently contracts with following firm for non-hazardous waste disposal:

Ogden Martin
Okahumpka FL
Air Permit A035193817 (Renewal filed 12/96)
Solids Permit S035279397 (Expires 12/18/00)

Waste waters from equipment cleaning, processing residues, and the contents of rejected and returned product will be filtered and neutralized in Bausch & Lomb's waste water processing tanks, then discharged into the City of Tampa POTW (sewer) under

Bausch & Lomb Pharmaceuticals, Inc.
Tampa FL
Industrial Wastewater Discharge Permit 1072 (Expires 5/31/98)

A copy of this permit is provided in the appendix.

Packaging wastes generated during production or from return goods are segregated as plastics or paper and may be recycled at any of several local private recycling facilities, including

BFI Recycling Services
Clearwater FL

There are no regulated air, water, or solid waste emission or substance parameters for the production of LE 0.2%. No OSHA-regulated components are present in the formulation.

The production and related handling of LE 0.2% at the Bausch & Lomb facility will not pose a threat to any endangered species nor to any registered National Historic Preservation Sites.

c. **Consumer Use**

As is true of any drug, a portion of LE 0.2% is excreted by the user. Nearly all of the excreted material is in the form of metabolites.

The following equation is used to calculate the maximum expected environmental concentration (MEEC) or sewer concentration of loteprednol etabonate entering the front end of a wastewater treatment plant

MEEC (ppm) = A X B X C X D X E X F

A = kg/year production
B = year/365 days
C = day person/567.81liters (daily sewer usage)
D = 1/246 x 10^6 people (U.S. population)
E = 10^6 mg/kg (conversion factor)
F = 1 million

For LE 0.2%, with an anticipated associated maximum annual production of 50 kg loteprednol etabonate, the MEEC may be calculated as follows:

MEEC = 1.96 x 10^{-8} x 50 kg (maximum annual production)

= 9.8 x 10^{-7} mg/L (ppm)

This value is the MEEC of loteprednol etabonate entering a WWTP; it does not reflect any depletion mechanisms such as biodegradation, hydrolysis or photosynthesis. The molecular structure indicates that LE should be susceptible to hydrolysis and biodegradation. Human metabolism will also affect the above relationship by depleting concentrations of LE with subsequent conversion to two polar metabolites PJ-90 and PJ-91 (see Item 5c).

7. Fate of Emitted Substances

This item not required under 21 CFR § 25.31 a (b).

8. Environmental Effects of Released Substances

This item not required under 21 CFR § 25.31 a (b).

9. Use of Resources and Energy

This item not required under 21 CFR § 25.31 a (b).

10. Mitigation Measures

This item not required under 21 CFR § 25.31 a (b).

11. Alternatives to the Proposed Action

This item not required under 21 CFR § 25.31 a (b).

12. List of Preparers

Anna Wysowskyj, MBA
Manager Regulatory Affairs
Bausch & Lomb Pharmaceutical, Inc.

Danny O. Helton, PhD
Senior Director Product Development
PHARMOS Corporation

13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for the preparation of the environmental assessment.

Date 12/19/96

Signature of Responsible Official Danny O. Helton

Title Senior Director Product Development

14. References

None

15. Appendix

MSDS - Loteprednol Etabonate Drug Substance

MSDS - Loteprednol Etabonate 0.2% Ophthalmic Suspension

Compliance Statement - SIPSY (France)

Certificate of Compliance - Ministry of the Environment (Loire Region)

Applicable Regulations - SIPSY (France)

Compliance Statement - Bausch & Lomb Pharmaceuticals, Inc. (Tampa)

Wastewater Discharge Permit 1072 - City of Tampa

Appendix

BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTEPREDNOL ETABONATE 0.2% OPHTHALMIC SUSPENSION

MATERIAL SAFETY DATA SHEET

Issued:
Revised: 1/06/97

Prepared by: Harold H. Shlevin, Ph.D.
VP - Research & Development

1. PRODUCT AND COMPANY IDENTIFICATION

Product Name: LOTEMAX - Allergy (interim name)
Generic Name: Loteprednol Etabonate
Ophthalmic Suspension, 0.2% (Sterile)
NDC No.: 24208-353-25, 24208-353-05, 24208-353-10

Legal Category: Prescription only medicine, filled in dropper-tipped plastic bottle suitable for dispensing, and overpacked inside a cardboard carton.

Drug Composition: Glucocorticoid

Company: BAUSCH & LOMB PHARMACEUTICALS, INC.
8500 Hidden River Parkway
Tampa, FL 33637 USA
Information: (800) 323-0000 (M-F) 8 a.m. - 5 pm EST
Emergency: (800) 227-1427

2. COMPOSITION/INFORMATION ON INGREDIENTS

Description	CAS#	TLV(mg/m^3)	PEL(mg/m^3)	% Content
Loteprednol Etabonate	82034-46-6	NE	NE	0.2
Glycerin	56-81-5	10	NE	≥1
Povidone	9003-39-8	NE	NE	>1
Purified Water	NA	NE	NE	≥1

Ingredients <1%: Tyloxapol, Edetate Disodium, Benzalkonium Chloride

3. HAZARDS IDENTIFICATION

BAUSCH & LOMB PHARMACEUTICALS
MSDS: LOTEPREDNOL ETABONATE 0.2% OPHTHALMIC SUSPENSION

****

EMERGENCY OVERVIEW

Plastic bottle in cardboard box. Milky white suspension. Toxic by ingestion.

****

POTENTIAL HEALTH HAZARDS

Carcinogenicity:
(NTP) No (IARC) No (OSHA) No

Eye: May cause irritation, burning sensation on instillation and hypersensitivity (anaphylactic) in some individuals. Studies in animals indicate that topical adrenocoids, when used in large amounts, can be systemically absorbed and can cause fetal abnormalities. Clinical studies indicate that ocular applied loteprednol etabonate (0.5%) does not result in detectable plasma drug levels.

Systemic: Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Systemic toxicity reactions include reversible hypothalamic-pituitary-adrenal axis gland suppression, manifestations of Cushing's syndrome, intercranial hypertension, hyperglycemia and glycosuria in some patients.

Skin: May cause irritation and localized hypersensitivity in some individuals with itching, swelling and diffused redness of the skin.

Ingestion: May cause irritation and hypersensitivity in some individuals. Large doses can induce vomiting, diarrhea, adrenal gland suppression, Cushing's syndrome, water retention, electrolyte imbalance and hyperglycemia.

Inhalation: May cause irritation and hypersensitivity in some individuals.

Chronic Effects: May cause hypersensitivity. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACTH stimulation. Prolonged ocular use can result in elevation of intraocular pressure, with damage to the optic nerve, defects in visual acuity and fields of vision and/or in posterior subcapsular cataract formation. It may also aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissues.

Target Organs: Eyes, skin, digestive tract, kidney and brain.

Medical Conditions Aggravated by Long Term Exposure:

* Anaphylactic cross-reactions may occur for glucocorticoids.
* Preexisting conjunctival or systemic fungal infections may be aggravated.
* Appropriate measures should be taken if this occurs.
* Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and other viral diseases of the cornea and conjunctiva.
* Tuberculosis of the eye.
* Fungal diseases of the ocular structures.
* Hypersensitivity to any of the ingredients of the medication.
* Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation.
* Acute purulent untreated infection of the eye can be masked or activity enhanced by the presence of corticosteroid medication.

4. FIRST AID MEASURES

Eyes: Rinse immediately with copious amounts of water for at least 20 minutes. Contact a physician.

Skin: Remove all contaminated clothing and wash skin with copious amounts of water for at least 20 minutes. Contact physician if skin becomes irritated.

Ingestion: Wash out mouth. Give plenty of water and bland fluids. Do not give anything to an unconscious person. Contact physician.

Inhalation: Remove person to fresh air, and if breathing stops, use artificial respiration. Contact physician.

Note to Physicians: None

5. FIRE FIGHTING MEASURES

Flammable Properties:
Flash point: NE Method: NE

Hazardous Products: Emits toxic fumes.

Extinguishing Media: Dry chemical, carbon dioxide, halon, water spray or fog, and foam on surrounding materials.

Fire fighting Instructions: Wear self-contained breathing apparatus and protective clothing. Use water spray to keep fire-exposed containers cool.

6. ACCIDENTAL RELEASE MEASURES

Large/Small spills: Use personal protective equipment. Contain the spill to prevent drainage into sewers, drains or streams. Use absorbent material to solidify the spill. Shovel or scoop up solidified waste. Dispose of material according to Federal, State and Local regulations.

7. HANDLING & STORAGE

Handling: Avoid contact with product and use caution to prevent puncturing containers. No special protective equipment or procedures are required in the clinical or home environment.

Storage: Store product upright in original containers with the cap tightly closed at a controlled room temperature 15°-30°C (59°-86°F). KEEP THIS AND ALL OTHER DRUGS OUT OF THE REACH OF CHILDREN.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering Controls: In the manufacturing plant, provide adequate ventilation for the raw material handling and compounding process which will maintain the dust and vapor levels below the TLV, STEL, and PEL values for the ingredients. Use of suitable respiratory protection equipment is recommended when handling the raw material. Ventilation fans should be explosion proof. Use adequate ersonal protective equipment, e.g. NIOSH-approved respirators, goggles or safety glasses, gloves and protective clothing. Ensure training in the handling of the chemical materials and use current Material Safety Data Sheets.

Eye Protection: (29 CFR 1910.133) Recommend goggles or chemical safety glasses.

Skin Protection: Thick impermeable gloves and protective clothing.

Respiratory Protection: (29 CFR 1910.134) NIOSH approved respirator recommended for handling raw materials. Warning: Do not use air purifying respirators in oxygen depleted environments. No respiratory protection is required in the clinical or home environment.

Other: None

Ventilation: Recommended

Contaminated Equipment: Wash contaminated clothing separately. Wash equipment with soap and water. Release rinse water into an approved wastewater system or according to Federal, State and Local regulations.

9. PHYSICAL & CHEMICAL PROPERTIES

Appearance & Odor:	Milky white suspension.		
Boiling Point:	NE	Evaporation Rate:	NE
Specific Gravity	1.0	Vapor Density:	NE
Vapor Pressure:	NE	Viscosity:	NE

10. STABILITY & REACTIVITY

Chemical Stability: Stable

Conditions to avoid: Extreme heat or cold.

Incompatibility: This product has the incompatibilities of water e.g. strong acids, bases, alkali metals, alkali hydrides.

Hazardous Decomposition Products: Emits toxic fumes.

Hazardous Polymerization: Should not occur.

11. TOXICOLOGY INFORMATION

Summary of Risks: Toxicological information refers to the raw materials of the product. Concentrations and toxicological effects are substantially reduced in the product. For more detailed information see MSDS on chemical material.

CAS #

82034-46-6 Loteprednol Etabonate

May cause irritation to the eyes, skin and respiratory tract. Can cause hypersensitivity (anaphylactic) in some individuals. Adverse reactions to corticosteroids include suppression of adrenal gland secretion, Cushing's syndrome, water retention, electrolyte imbalance and hyper-glycemia. Studies in animals indicate that topical adrenocorticoids, when used in large amounts, can be

systemically absorbed and can cause fetal abnormalities. Immune suppression may result from chronic high doses.

56-81-5 Glycerin

May cause irritation to eyes and skin. Repeated or prolonged exposure can cause dermatitis or eye conjunctivitis. Inhalation is not likely due to low evaporation rate, but fumes may cause irritation and defatting of the tissues. Ingestion can cause headache, restlessness, insomnia, dizziness, vomiting, diarrhea and fever. Large doses can cause hemolysis, hemoglobinuria, hyperglycemia, glycosuria, renal failure, convulsions, narcosis and paralysis. Oral-rat LD_{50} 12,600 mg/kg. Decomposition release corrosive fumes of acrolein. Avoid open flame and extreme heat. Incompatibilities include strong acids, strong oxidizers, metal oxides and metal hydrides.

9003-39-8 Povidone

Acute: prolonged or repeated contact may cause skin or eye irritation. Inhalation may result in respiratory irriation. Ingestion may result in gastric disturbances.
Chronic: Due to presence of a synthetic by product, chronic over-exposure may result in liver or kidney injury.

12. ECOLOGICAL INFORMATION

Chemical Fate Information: Product administered to patients presents a negligible impact on the environment.

13. DISPOSAL CONSIDERATIONS

Dispose of material according to Federal, State, and Local regulations. The method typically used is incineration.

Transportation Data: DOT SHIPPING CLASSIFICATION: WASTE CONSUMER COMMODITY

EPA Designations: RCRA Hazardous Waste: Not Listed

SARA Title III: Not Listed

14. TRANSPORT INFORMATION

Transportation Data: DOT SHIPPING CLASSIFICATION: CONSUMER COMMODITY

15. REGULATORY INFORMATION

EPA Designations: RCRA Hazardous Waste (40 CFR 261.33) Not Listed

FDA Designations: Prescriptions only medication. NDC No. Not available.

OSHA Designations: (29 CFR 1910.1000, Table Z) Not Listed

SARA Title III: Not Listed

16. OTHER INFORMATION

None

The information contained herein is furnished without warranty of any kind. The above information is believed to be correct but does not purport to be all inclusive and should be used only as a guide. Users should make independent determinations of the suitability and completeness of information from all sources to assure proper use and disposal of these materials and the safety and health of employees and customers.

NE - Not Established
< - Less Than
> - Greater Than

SIPSY FRANCE

F - ENVIRONMENTAL IMPACT ANALYSIS

We certify that LOTEPREDNOL ETABONATE manufactured by SIPSY FRANCE is produced according to the local regulations concerning :

- safety of workers
- safety of installations
- waste disposal
- environmental agency

The plant is regularly inspected by our local representatives to check the compliance with these regulations

GENERAL MANAGER OF SIPSY

JF. MARCOPOULOS

Pharmaceutical Division | 8500 Hidden River Parkway, Tampa FL 33637 | 813 975 7700, Fax 813 975 7770

BAUSCH & LOMB
Healthcare and Optics Worldwide

December 19, 1996

Compliance Statement

Bausch & Lomb Pharmaceuticals, Inc. states that it is in full compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of

loteprednol etabonate 0.2% ophthalmic suspension

at its facilities in Tampa FL as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of loteprednol etabonate 0.2% ophthalmic suspension at its facilities in Tampa FL.

Anthony Caracciolo
Vice President, Operations.

Industry Name Bausch & Lomb Pharmaceutical Permit No. 1072

Acceptance of Permit

Bausch & Lomb Pharmaceutical accepts the conditions of the permit and
(name of company)

agrees to meet the conditions herein.

Permit period: June 1, 1996 through May 31, 1998

By _____ 6/26/96
(signature) (date)

*Name Anthony Caracciolo

Title Vice-President of Operations

* Must be the owner or an authorized representative of the company.

(Return this signed page to the Industrial Waste Division)

CITY OF TAMPA

Department of Sanitary Sewers

Howard F. Curren
Advanced Wastewater Treatment Plant

Mr. Anthony Caracciolo
Bausch & Lomb Pharmaceutical
8500 Hidden River Parkway
Tampa, FL 33637

June 18, 1996

Re: Issuance of a Wastewater Discharge Permit to Bausch & Lomb Pharmaceutical, by the City of Tampa, Department of Sanitary Sewers.

Dear Mr. Caracciolo:

The enclosed issued permit, No. 1072, governs the wastewater discharge from the facility located at 8500 Hidden River Parkway, Tampa, Florida 33637, into the City of Tampa's wastewater collection system. All discharges from this facility and actions and reports relating thereto shall be in accordance with the terms and conditions of this permit.

The discharge permit is attached to this letter. I am enclosing two copies of the front page of the discharge permit with a block reserved for your signature indicating acceptance of the limitations and conditions specified in this permit. Please sign both copies of the front page of the permit and return one of the signed copies to John M. Daily, City of Tampa, Industrial Waste Division, 2700 Maritime Blvd., Tampa, FL 33605.

If you have any questions about this permit please do not hesitate to contact John M. Daily at 247-3451.

Sincerely,

Ralph L. Metcalf II, P.E.
Director
Department of Sanitary Sewers

RLM:jmd

2700 Maritime Boulevard • Tampa, Florida 33605 • 813/247-3451 • Fax: 813/248-5269

CITY OF TAMPA

DEPARTMENT OF SANITARY SEWERS

INDUSTRIAL WASTEWATER DISCHARGE PERMIT

10 027

City of Tampa

Department of Sanitary Sewers

Industrial Wastewater Discharge Permit

Cover Page

Permit No. 1072

In accordance with the provisions of Section 26-122 of the City of Tampa Code:

Company Name Bausch & Lomb Pharmaceutical

Address 8500 Hidden River Parkway

Telephone Number 975-7700

Name of Applicant Anthony Caracciolo

Is hereby authorized to discharge industrial wastewater from the above identified facility and through the outfalls identified herein into the City of Tampa sewer system in accordance with the conditions set forth in this permit. Compliance with this permit does not relieve the permittee of its obligation to comply with any or all applicable pretreatment regulations, standards or requirements under local, State, and Federal laws, including any such regulations, standards, requirements, or laws that may become effective during the term of this permit.

Noncompliance with any term or condition of this permit shall constitute a violation of the City of Tampa sewer use ordinance.

This permit shall become effective on June 1, 1996
and shall expire at midnight on May 31, 1998

If the permittee wishes to continue to discharge after the expiration date of this permit, an application must be filed for a renewal permit a minimum of 90 days prior to the expiration date.

Director — Date
Department of Sanitary Sewers

10 028

PART 1 - APPLICABLE EFFLUENT LIMITATIONS

SECTION 1 - EFFLUENT DISCHARGE LIMITS

A. During the period of this permit, the permittee is authorized to discharge process wastewater to the City of Tampa from only the outfalls listed below.

Description of outfalls:

Outfall	Description
001	Outfall 001 is the manhole located in the grass at the southwest corner of the facility. All process, laboratory, and sanitary wastewater is discharged to the city of Tampa from this outfall.
002	Outfall 002 is the manhole located in the grass on the east side of the facility. Only the process wastewater storage tanks discharge to this manhole.
003	Outfall 003 is the manhole located in the grass on the east side of the facility. Only the neutralizing basin discharges to this manhole.

B. During the period of this permit the discharge from outfall 002 must comply with the following pretreatment regulations established in 40 CFR Part 439 (Pharmaceutical Manufacturing Point Source Category), Subparts C and D.

40 CFR Part 439 - Pharmaceutical Manufacturing Point Source Category
Subpart C - Chemical Synthesis Products Subcategory,
439.37 - Pretreatment Standards for New Sources (PSNS), and
Subpart D - Mixing/Compounding and Formulation Subcategory,
439.47 - Pretreatment Standards for New Sources (PSNS)

Pollutant	Max for any 1 day (mg/l)	Average of daily values for 30 consecutive days (mg/l)
Total cyanide	33.5	9.4

C. During the period of this permit the discharge from outfall 001 shall not exceed the following effluent limitations. In addition, the discharge shall comply with all applicable regulations and standards contained in chapter 26, City of Tampa code.

Parameter	Daily Max. (mg/l)	Monthly Avg. (mg/l)
Arsenic, (As)	0.1	0.05
Barium, (Ba)	10.0	5.0
Cadmium, (Cd)	0.4	0.2
Chromium, (Cr, total)	5.0	2.5
Copper, (Cu)	3.6	1.8
Lead, (Pb)	0.6	0.3
Manganese, (Mn)	2.0	1.0
Mercury, (Hg)	0.01	0.005
Nickel, (Ni)	3.6	1.8
Selenium, (Se)	0.04	0.02
Silver, (Ag)	1.0	0.5
Zinc, (Zn)	3.6	1.8
Oil & Grease	100.0	100.0
Cyanide, Total	1.0	1.0
pH	6.0 - 11.0	6.0 - 11.0
Total Purgeable Organics	100 ug/l	100 ug/l
Base/Neutrals and Acids	MDL	MDL

PART 2 - MONITORING AND REPORTING REQUIREMENTS

SECTION 1 - MONITORING REQUIREMENTS

A. During the period of this permit, the permittee shall monitor outfall 001 for the following:

Parameter	Location	Frequency	Sample Type
Flow, gpd	(1)	Monthly	(2)
pH	(1)	(3) Semi-annually	(4) Grab
Cadmium, mg/l	(1)	(3) Semi-annually	(4) Composite
Chromium, mg/l	(1)	(3) Semi-annually	(4) Composite
Copper, mg/l	(1)	(3) Semi-annually	(4) Composite
Lead, mg/l	(1)	(3) Semi-annually	(4) Composite
Nickel, mg/l	(1)	(3) Semi-annually	(4) Composite
Zinc, mg/l	(1)	(3) Semi-annually	(4) Composite
Total Cyanide, mg/l	(5)	(3) Semi-annually	(4) Grab
Purgeable Organics	(1)	(3) Semi-annually	(4) Grab
Base/Neutrals and Acids	(1)	(3) Semi-annually	(4) Grab
Base and Neutral Extractables			
Polychlorinated Biphenyls			
Acid Extractables			
Additional Extractables			

(1) - Outfall 001

(2) - Flows shall be read on the first business day of each month from the permittees wastewater discharge flow meter.

(3) - April, October

(4) - Definitions of sample types are located in PART 4 SECTION 1 of this permit.

(5) - Outfall 001 and outfall 002

B. All activities related to sampling and analysis shall comply with Chapter 62-160, F.A.C. Sampling activities and laboratory analyses shall be performed according to procedures specified in "The Department of Environmental Regulation Standard Operating Procedures for Laboratory Operations and Sample Collection Activities" (DER-QA-001/92) September 1992 (see PART 4 SECTION 4 Paragraph A).. Alternatively, an organization with the required protocols listed in their Department Approved Comprehensive Quality Assurance Plan may sample and analyze according to the protocols specified in that document. Purgeable Organics shall be analyzed in accordance with EPA Method 624. Base/Neutrals and Acids shall be analyzed in accordance with EPA Method 625. The Method Detection Limits (MDL) for Purgeable Organics and Base/Neutrals and Acids shall be units of ug/l (micrograms per liter).

SECTION 2 - REPORTING REQUIREMENTS

A. Monitoring Reports

1. Analytical monitoring results obtained shall be summarized and reported as follows:

   a. Parameters monitored semi-annually shall be reported within the month following the reported period. The report shall also include the monthly process wastewater discharge flows and the average daily process wastewater discharge flow for the reported period

B. Pursuant to the reporting requirements of 40 CFR Part 403.12 (g), the results of all monitoring performed more frequently than required by this permit, using test procedures approved under 40 CFR Part 136, shall be submitted with the report.

C. When a self-monitoring report shows any violation of the applicable standards included in PART 1 of this permit, the permittee must resample and submit both results within 30 days of receiving original sample results, except the permittee is not required to resample if:

(1) The Control Authority performs sampling at the permittee at a frequency of at least once per month, or

(2) The Control Authority performs sampling at the permittee between the time when the permittee performs its initial sampling and the time when the permittee receives the results of this sampling.

The permittee must notify the Industrial Waste Division within 24 hours of receipt of monitoring results if the results indicate any violation of applicable standards.

D. Signatory requirements are established in PART 4 SECTION 4 (E) of this permit.

E. Accidental Discharge Report

1. The permittee shall notify the City of Tampa, Industrial Waste Section, immediately upon its having knowledge of the occurrence of an accidental discharge of substances regulated by this permit or prohibited by Chapter 26, City of Tampa Code. At all times the City of Tampa, Industrial Waste Section shall be notified by telephone at (813) 247-3451. The notification shall include location of discharge, date and time thereof, type of waste, including concentration and volume, and corrective actions taken.

2. Within five days following such notice, the permittee shall submit to the City of Tampa AWTP a detailed written report. The report shall specify:

   a. Description and cause of the upset, slug or accidental discharge, the cause thereof, and the impact on the permittee's compliance status. The description should also include location of discharge, type, concentration and volume of waste.

   b. Duration of noncompliance, including exact dates and times of noncompliance, and if the noncompliance continues, the time by which compliance is reasonably expected to occur.

   c. All steps taken or to be taken to reduce, eliminate, and prevent recurrence of such an upset, slug, accidental discharge, or other conditions of non-compliance.

   d. All reports required of this permit shall be submitted to:

City of Tampa
Industrial Waste Section
2700 Maritime Blvd.
Tampa, FL 33605.

PART 3 - SPECIAL CONDITIONS / COMPLIANCE SCHEDULES

1. None

PART 4 - STANDARD CONDITIONS

SECTION 1 - DEFINITIONS

A. AWTP - Advanced Wastewater Treatment Plant

B. Composite sample - shall mean a minimum of eight (8) grab samples collected at equally spaced one (1) hour intervals, per operating shift, and proportioned according to flow. The use of a properly operated automatic composite sampler is acceptable.

C. Daily maximum - the maximum allowable discharge concentration of pollutant during a calendar day.

D. Grab sample - for monitoring requirements, is defined as an individual sample which is taken from a waste stream on a one-time basis with no regard to the flow in the waste stream and without consideration of time. Daily pH monitoring may be performed by either grab sample or continuous pH electrometric probe monitoring.

E. Monthly average - the maximum allowable value for the average of all observations obtained during one calendar month.

F. POTW - Publicly Owned Treatment Works

SECTION 2 - GENERAL CONDITIONS

A. Duty to Comply

The permittee must comply with all conditions of this permit. Failure to comply with the requirements may be grounds for administrative action, or enforcement proceedings including civil or criminal penalties, injunctive relief and summary abatements.

B. Duty to Mitigate

The permittee shall take all reasonable steps to minimize or correct any adverse impact on the environment, public health or POTW resulting from noncompliance with this permit, including such accelerated or additional monitoring as necessary to determine the nature and impact of the non-complying discharge.

C. Permit Action

This permit may be modified, revoked and reissued, or terminated for causes including, but not limited to, the following:

- Violation of any terms or conditions of this permit;

- Transfer of ownership;

- Obtaining this permit by misrepresentation or failure to disclose fully all relevant facts;

- A change in any condition of the discharge that requires either a temporary or permanent reduction or elimination of the authorized discharge;

- Information indicating that the permitted discharge poses a threat to human health or welfare, or property real;

- Upon request of the permittee, provided such request does not create a violation of any existing applicable requirements, standards, laws, or rules and regulations;

- Material or substantial alterations or additions to the dischargers operation that adversely impact the wastewater discharge and which were not in existence as of the date of the issued permit;

- To incorporate any new or revised Federal, State, or City pretreatment standards or requirements, to protect the operation of the treatment plant;

- Wastewater discharge volumes that have an average change of 20% or more during a six month period. (For new industries, the baseline monitoring report can be used to determine if an average change in discharge volume has exceeded 20% during the first six months of operation.)

The filing of a request by the permittee for a permit modification, revocation and reissuance, or termination, or a notification of planned changes or anticipated noncompliance, does not stay any permit condition.

D. Property Rights

The issuance of this permit does not convey any property rights of any sort, or any exclusive privileges, nor does it authorize any injury to private property or any invasion of personal rights, nor any infringement of Federal, State or local laws or regulations.

E. Severability

The provisions of this permit are severable, and if any provision of this permit, or the application of any provision of this permit to any circumstance, is held invalid, the application of such provision to other circumstances, and the remainder of this permit, shall not be affected thereby.

F. Limitation on Permit Transfer

Wastewater discharge permits are issued to a specific user for a specific operation and are not assignable or transferable to any other user. The permittee must inform the City of Tampa at least thirty (30) days in advance of all proposed owner/operator transfers.

G. Dilution

No Permittee shall increase the use of potable or process water, or in any way attempt to dilute a discharge as a partial or complete substitute for adequate treatment to achieve compliance with the limitations contained in this permit.

H. Duty To Reapply

If the permittee desires to continue to discharge after the expiration of this permit, the permittee shall reapply on the application forms then in use at least ninety (90) days before this permit expires. Under no circumstances shall the permittee continue to discharge after the expiration of the permit, unless reapplication was submitted as required. Continued discharge under the conditions of the expired permit is authorized until the new permit is issued.

I. Personnel Safety

The permittee shall provide safe inspection conditions for city pretreatment program personnel and shall provide such personnel with all necessary safety information regarding the facility's safety policy pertaining to required personal safety gear.

SECTION 3 - OPERATIONS AND MAINTENANCE OF POLLUTION CONTROLS

A. Proper Operation and Maintenance

The permittee shall at all times properly operate and maintain all facilities and systems of treatment and control (and related appurtenances) which are installed or used by the permittee to achieve compliance with the conditions of this permit. Proper operation and maintenance includes but is not limited to: effective performance, adequate funding, adequate operator staffing and training, and adequate laboratory and process controls, including appropriate quality assurance procedures. This provision requires the operation of back-up or auxiliary facilities or similar systems only when necessary to achieve compliance with the conditions of the permit.

B. Duty to Halt or Reduce Activity

Upon reduction, loss or failure of the pretreatment facility, the permittee shall, to the extent necessary to maintain compliance with its permit, control production or all discharges or both until operation of the pretreatment facility is restored. It shall not be a defense for a permittee in an enforcement action that it would have been necessary to halt or reduce the permitted activity in order to maintain compliance with the conditions of this permit.

C. Bypass of Treatment Facilities

1. Bypass is prohibited unless it is unavoidable to prevent loss of life, personal injury or severe property damage or no feasible alternative exists.

2. Bypass not exceeding limitations. The permittee may allow any bypass to occur which does not cause effluent limitations to be exceeded, but only if it also is for essential maintenance to assure efficient operation.

3. Notification of bypass:

a. Anticipated bypass. If the permittee knows in advance of the need for a bypass, it shall submit prior written notice, if possible at least ten days before the date of the bypass, to the City of Tampa AWTP (addresses specified in PART 2 SECTION 2 (E) of this permit).

b. Unanticipated bypass. The permittee shall immediately notify the City of Tampa AWTP and submit a written notice to the City of Tampa AWTP within five days of the bypass as specified in PART 2 SECTION 2 (E) of this permit.

D. Removed Substances

Solids, sludges, filter backwash, or other pollutants removed in the course of treatment or control of wastewaters shall be disposed of in accordance with section 405 of the Clean Water Act and Subtitles C and D of the Resource Conservation and Recovery Act.

SECTION 4 - MONITORING AND RECORDS

A. Representative Sampling

Samples and measurements taken as required herein shall be representative of the volume and nature of the monitored discharge. The sampling shall be done on a day of normal to maximum process operation. All samples shall be taken at the monitoring points specified in this permit and, unless otherwise specified, before the effluent joins or is diluted by any other wastestream, body of water or substance. Monitoring points shall not be changed without notification to and the approval of the City of Tampa.

B. Inspection and Entry

The permittee shall allow the City of Tampa, or an authorized representative, upon the presentation of a City of Tampa employee photo-identification card, to:

- Enter upon the permittee's premises where a regulated facility or activity is located or conducted, or where records must be kept under the conditions of this permit;

- Have access to and copy any records that must be kept under the conditions of this permit;

- Inspect any facilities, equipment (including monitoring and control equipment), practices, or operations regulated or required under this permit;

- Sample or monitor, for the purposes of assuring permit compliance, any substances or parameters at any location;

- Inspect any production, manufacturing, fabricating or storage area where pollutants, regulated under the permit, could originate.

C. Retention of Records

1. The permittee shall retain records of all monitoring information, including all calibration and maintenance records, all original strip chart recordings for continuous monitoring instrumentation, copies of all reports required by this permit, and records of all data used to complete the application for this permit, for a period of at least three years from the date of the sample, measurement, report or application. This period may be extended by request of the City of Tampa at any time.

2. All records that pertain to matters that are the subject of special orders or any other enforcement or litigation activities brought by the City of Tampa shall be retained and preserved by the permittee until all enforcement activities have concluded and all periods of limitation with respect to any and all appeals have expired.

D. Record Contents

Records of sampling information shall include:

- The date, exact place, time and methods of sampling or measurements, and sample preservation techniques or procedures;

- Who performed the sampling or measurements;

- The date(s) analyses were performed;

- Who performed the analyses;

- The analytical techniques or methods used;

- The results of such analyses; and

- Proper chain of custody documentation.

E. Signatory Requirements

All applications, permits, reports or information submitted to the City of Tampa shall be signed and certified as indicated below:

1. By the owner or an authorized representative of the industrial user. An authorized representative of an industrial user shall mean:

   a. A president, secretary, treasurer or vice president of a corporation in charge of a principal business function, or any person who performs a similar policy-or decision-making function for the corporation.

   b. A manager of one or more manufacturing, production or operation facilities employing more than 250 persons, or having gross annual sales or expenditures exceeding $25 million dollars, if authority to sign documents has been assigned or delegated to the manager in accordance with corporate procedures.

   c. A general partner or proprietor if the industrial user is a partnership or sole proprietorship respectively.

   d. A duly authorized representative of a person indicated in (a), (b) or (c) above if authorization has been made in writing on a prescribed authorization form submitted to the City of Tampa Industrial Waste Section. (Should authorization no longer be accurate because a different individual or position has responsibility for environmental matters for the company, a new authorization form for the new representative must be submitted to the City of Tampa Industrial Waste Section.)

2. Certification. Any person signing a document required by this permit shall make the following certification:

   "I certify under penalty of law that I am familiar with the information contained in this report and its attachments and that to the best of my knowledge and belief such information is true, complete and accurate."

3. Any change in signature shall be submitted to the City of Tampa writing within 30 days after the chang

F. Falsifying Information

Knowingly making any false statement on any report or other document required by this permit, o knowingly rendering any monitoring device or method inaccurate, or not sampling a representativ wastewater stream, may result in punishment under criminal law proceedings as well as being subjected t civil penalties and injunctive relief.

SECTION 5 - ADDITIONAL REPORTING REQUIREMENTS

A. Planned Changes

The permittee shall give notice to the City of Tampa 90 days prior to any facility expansion, productio increase, or process modifications which results in new or increased discharge volumes that have an averag change of 20% or more, over a six month period or which results in a change in the nature of the discharge The baseline monitoring report can be used to determine if an average change in discharge volume o production has exceeded 20% during the first six months of operation.

B. Duty to Provide Information

The permittee shall furnish to the City of Tampa, within a reasonable time, any information which the City of Tampa may request to determine whether cause exists for modifying, revoking and reissuing, or terminating this permit, or to determine compliance with this permit. The permittee shall also furnish to the City of Tampa upon request, copies of records required to be kept by this permit.

SECTION 6 - ENFORCEMENT

A. Recovery of Costs Incurred

The permittee violating any of the provisions of this permit, Chapter 26, City of Tampa Code, or causing a discharge producing a deposit or obstruction, or causing damage to or otherwise inhibiting the City's wastewater disposal system shall be liable to the City for any expense, loss, or damage caused by such violation or discharge. The City shall bill the permittee for the costs incurred for any cleaning, repair, or replacement work caused by the violation or discharge. Refusal to pay the assessed costs shall constitute a violation of this permit and Chapter 26, City of Tampa Code.

AUTHORIZATION OF APPROVED REPRESENTATIVE

Industrial User Name: Bausch & Lomb Pharmaceutical

Address: 8500 Hidden River Parkway

Tampa, FL 33637

Date: June 26, 1996

Discharge Permit No. 1072

To:

Industrial Waste Division
City of Tampa
2700 Maritime Blvd.
Tampa, FL 33605

I, Anthony Caracciolo, hereby certify that I am a responsible corporate officer, manager, general partner or proprietor of the above named company and that I am in charge of principal business functions and am able to perform policy and decision making functions for the company.

I hereby duly authorize Elizabeth Ortiz, whose signature also appears below to be my representative. I authorize my representative to sign all Industrial Pretreatment self-monitoring certification statements on my behalf.

Signed

Title Vice President, Operations

Signature of Authorized Representative

Title of Representative Environmental Health & Safety Officer