CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20545

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

MAY 22 1995

DF

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PROCANBID CONTROLLED RELEASE TABLETS (500 and 1000 mg)

NDA 20-545

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MAY 22 1995

FINDING OF NO SIGNIFICANT IMPACT NDA 20-545

PROCANBID CONTROLLED RELEASE TABLETS
(500 and 1000 mg)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decision maker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues.

WARNER-LAMBERT COMPANY, MORRIS PLAINS, NJ 07950 has conducted a number of environmental studies and prepared an environmental assessment according to 21 CFR § 25.31a - Format 1.(a) to support their New Drug Application # 20-545. The assessment covers the manufacture of the bulk drug substance and drug product, packaging and disposal.

The manufacturing facility for the bulk drug substance is:

PARKE-DAVIS HOLLAND CHEMICAL FACILITY, HOLLAND, MI

The manufacturing facility for the finished dosage form is:

WARNER-LAMBERT/PARKE-DAVIS, MORRIS PLAINS, NEW JERSEY

Solid waste is incinerated in the following facilities:

ADVANCED ENVIRONMENTAL TECHNOLOGY CORP, FLANDERS, NJ
LAIDLAW ENVIRONMENTAL SERVICES INC, LAUREL, MD
ADIRONDACK RESOURCE RECOVERY FACILITY, HUDSON FALLS, NY
OGDEN MARTIN INCINERATORS, ALEXANDRIA-FAIRFAX, VA

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of these operations and concluded that they will not have a significant effect on the quality of the human environment and that it is not necessary to prepare an environmental impact statement.

Precautions taken at the sites of manufacture are expected to minimize occupational exposures and environmental releases. These include the normal devices to control emissions, good occupational health and safety standards for employees, and other measures reflecting compliance with requirements of applicable permits, consent decrees and administrative orders at all levels of government.

PROCANBID CONTROLLED RELEASE TABLETS (500 and 1000 mg) are administered orally for the treatment of arrhymias in cardiac patients. The drug and its metabolites are expected to be excreted into publicly owned treatment works (POTWs).

Chemical and physical data indicate that the drug and its degradation products will be in the aquatic compartment, however they are not toxic to Daphnia magna and do not inhibit microbial growth at concentrations many times greater than the maximum expected environmental concentration (MEEC).

Disposal of unqualified, returned or expired lots will be done at licensed incinerators. American hospitals and clinics may dispose empty and partially used packages according to their standard operating procedures and regulations.

Significant adverse effects are not expected on endangered or threatened species or on property listed in or eligible for listing in the National Register of Historic Places.

This FONSI states that the Center for Drug Evaluation and Research finds that all operations can be conducted without any significant adverse environmental effects.

/S/ April 7, 1995

Prepared by FLORIAN ZIELINSKI, Ph.D., HFD-110 Date

/S/ 5/19/95

PHILLIP G. VINCENT, Ph.D. Date
Environmental Assessment Officer

/S/ 5/22/95

ROBERT A. JERUSSI, Ph.D. Date
Associate Director for Chemistry
CDER

Original: NDA 20-545
cc: HFD-110 F Zielinski
HFD-102 P Vincent
HFD-110 CSO
HFD-110 Div. File
RD init by R Wolters 4-10-95
word perfect file FONSI#20552

CC: Original NDA 20-545/HFD-110 CSO copy to NDA 20-545
FONSI File 20545
HFD-019

F/T May 19, 1995

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ENVIRONMENTAL ASSESSMENT

(FOI Environmental Assessment Information)

Environmental Impact Analysis Report

An environmental assessment has been prepared in accordance with the requirements stated in 21 CFR Part 25.31a.

3.14. Environmental Assessment - Procanbid™ 500- and 1000-mg Controlled-Release Tablets

3.14.1. Date

December 1, 1994

3.14.2. Name of Applicant

Warner-Lambert Company

3.14.3. Address

201 Tabor Road
Morris Plains, NJ 07950

3.14.4. Description of the Proposed Action

3.14.4.1. Requested Action

Warner-Lambert has filed a New Drug Application for Procanbid (procainamide 500- and 1000-mg controlled-release tablets). The drug substance is procainamide hydrochloride, an active ingredient currently used in numerous approved drug products in the United States and recognized in the current United States

Pharmacopeia. The New Drug Application requests approval of Procanbid for the treatment of arrhythmias in cardiac patients.

3.14.4.2. Need for Action

Approval of this application will result in production and distribution of Procanbid 500- and 1000-mg controlled-release tablets in the United States. Approval will offer patients in the United States an alternative dosing schedule for treatment of cardiac arrhythmias. Because of the benefits associated with a more convenient dosing schedule for patients and the increased probability of patient compliance with the recommended dosage regimen, approval is sought and preferable to nonapproval. Estimates of the quantity of procainamide to be produced have been submitted in air emission permit applications to the Michigan Department of Natural Resources (MDNR) for the procainamide hydrochloride synthetic process. If additional quantities are required to supply the market, additional air emission permit applications will be filed to the appropriate authorities.

3.14.4.3. Sites of Production

Bulk drug substance will be manufactured at the following Warner-Lambert facilities:

Parke-Davis Holland Chemical Facility
188 Howard Avenue
Holland, MI 49424

Drug product formulation, packaging, testing, and release will be performed at the following Warner-Lambert facility:

Warner-Lambert/Parke-Davis
182 Tabor Road
Morris Plains, NJ 07950

3.14.4.4. Environmental Settings of Warner-Lambert Manufacturing Locations

The environmental settings of the Warner-Lambert drug substance and drug product manufacturing and packaging facilities are as follows:

3.14.4.4.1. Parke-Davis Holland Chemical Facility

The Parke-Davis Holland Chemical facility is located on approximately 50 acres of land in the Township of Holland (1990, Population 17,523), in Ottawa County, Michigan, approximately 30 miles west of Grand Rapids. The site consists of approximately 15 buildings and employs an average work force of 300 employees. It is adjacent to the Macatawa River near the river's confluence with Lake Macatawa. Lake Macatawa flows into Lake Michigan approximately 4.5 miles downstream from the facility. The plant is located in an industrial and commercial area in which the surrounding neighborhood includes residential, light industry, retail business, and beech-maple forests. The site is just north of the city of Holland.

Air Resources

Ambient air quality at this facility is not routinely monitored. Indoor air quality is monitored. The facility has a number of other air permits that are associated with the specific batch manufacturing processes conducted at the site. Air emission permit applications have been submitted and approved for the individual steps of the procainamide hydrochloride manufacturing process. It should be noted that there are 2 alternative routes filed with the NDA for manufacturing procainamide hydrochloride drug substance. The air emission permit applications for the individual steps for both routes are submitted.

Water Resources

The Holland facility receives its potable water from Holland Township. Holland Township obtains its potable water from the city of Wyoming, the city of Holland, and in rural areas, from ground water. Wyoming obtains water from Lake Michigan via an intake structure located approximately 6 miles northwest of the facility and about 6 miles north of Lake Macatawa's outlet to Lake Michigan. The city of

Holland obtains its potable water from Lake Michigan via an intake located about 0.75 miles off-shore and about 5 miles west of the facility and 2 miles north of Lake Macatawa's outlet to Lake Michigan. The facility pumps its sanitary wastes to the Holland Municipal Waste Treatment Facility.

Process water for noncontact cooling is obtained from an intake located on the channel leading to the Macatawa River on the east side of the facility. This noncontact cooling water is discharged into the Macatawa River under NPDES Permit MI 0004715. Approval of this product will not exceed permit limits.

A storm water retention pond is located in the southwest corner of the site next to the Macatawa River. This pond receives surface runoff from the west part of the site, except runoff from certain roofs and all secondary containment areas which is sent to the chemical waste treatment system. The unlined retention pond has no outlet, but water leaves it through the soil. Water from this treatment system is disposed of by deepwell injection for which Permits MI-139-1W-0003, MI-139-1W-0004, and MI-139-1W-0005 have been granted. Approval of this product will not exceed permit limits.

Land Resources

The Holland facility is located on a former beach and associated offshore deposits of a higher stage of Lake Michigan. These areas have locustrine sand and gravel deposits and may include intercalated clay. Eolian sand and organic soils may be present. The area is in the Eastern Deciduous Forest Ecoregion, and the climax forest is beech-maple (Bailey, Robert G., 1978). The site slopes from a high in the north of 605 ft to the Macatawa River in the south, which has an approximate elevation of 579 ft. The site is mostly paved or covered by buildings.

Environmental Regulations

Air emissions are regulated by Michigan Act 348. Due to the batch nature of the facility operations, the agency (Michigan Department of Natural Resources - MDNR) issues air emissions control permits for entire manufacturing operations. Air emission

permit applications have been submitted and approved for the procainamide hydrochloride process.

Aqueous emissions are regulated by Michigan Minerals Wells Act. Safe Drinking Water Act, Clean Water Act, and the Resource Conservation and Recovery Act. Compliance with these statutes has been achieved by obtaining Underground Injection Control permits from US EPA MI-139-1W-0003, MI-139-1W-0004, and MI-139-1W-0005. For cooling water discharges, NPDES Permit MI 0004175 has been granted. Approval of this product will not exceed the limits for these permits.

Treatment and storage of hazardous wastes are regulated by Michigan Act 64 and the Resources Conservation and Recovery Act. A Michigan Act 64 license has been granted.

Off-site disposal of hazardous waste is performed in accordance with Michigan Act 64, Resource Conservation and Recovery Act, and the Hazardous Materials Transportation Act regulatory requirements. The State Historic Preservation Officer of Michigan has determined that the property does not require a historic property evaluation for installation of new equipment.

Warner-Lambert certifies that the Holland Chemical Facility is in substantial compliance with permit limits and environmental regulations.

3.14.4.4.2. Morris Plains Drug Product Formulation Facility

Warner-Lambert's Parke-Davis Morris Plains facility is located on approximately 110 acres in Morris Plains, in Morris County, New Jersey. The site consists of 4 buildings located on both sides of New Jersey Route 53 (Tabor Road). On the east side of Route 53 is the Warner-Lambert World Headquarters Building and a Consumer Products Research Building. On the west side of Route 53 is a Pharmaceutical Research and Development Building and the Manufacturing Building. The manufacturing building contains the Parke-Davis Pharmaceutical Manufacturing Operations, a research and development area, a pilot operations area, and a sales training center. The buildings on the west side of Route 53 are bounded by the

Watnong Brook and Conrail railroad tracks. General land use within a half-mile radius is mixed residential and commercial usage.

Air Resources

Parke-Davis Pharmaceutical Manufacturing Operations has obtained air permits issued by the New Jersey Department of Environmental Protection and Energy (NJDEPE). The air permits are for dust collection equipment which is used in conjunction with the weighing, milling, blending, tablet compression, coating solution manufacturing, and tablet coating operations employed in the manufacturing of tablets. The equipment is used for the manufacturing of other products also. The air permits are for a number of products.

Water Resources

The Parke-Davis Morris Plains Facility receives its potable water from the Southeast Morris County Municipal Utilities Authority (SMCMUA). The SMCMUA obtains its water from wells within the collection and distribution system. Water is drawn from the SMCMUA distribution system into the Warner-Lambert site distribution system. Water from the Warner-Lambert distribution system to be used for manufacturing pharmaceutical products undergoes deionization.

The wastewater from the cleaning of manufacturing contact and cleaning is discharged to an on-site wastewater treatment plant where primary and secondary treatment is performed. The wastewater treatment effluent is combined with sanitary wastewater prior to discharge to the Township of Morris sanitary sewer system.

Land Resources

The portion of the Morris Plains Facility located to the west of Route 53 was farmland until 1945. The property was purchased by the Maltine Company, a manufacturer of emulsified corn syrup and cod liver oil. The Maltine Company became Chilcott Laboratories and merged with Warner-Lambert in 1953. The majority of the soils in the area are urban land (Ua). The soils have been extensively reworked that the original profile is not identifiable. Ua soils are mostly well

drained, deep sandy, gravely or stoney material of assorted glacial deposits. The site is on a relatively flat land with an elevation of 440 ft above sea level.

Environmental Regulations

Air emissions are regulated by the New Jersey Department of Environmental Protection and Energy, Division of Environmental Quality. The applicable regulations are N.J.A.C., Subchapters 1 to 25. A permit application is submitted to NJDEPE prior to installation of new equipment or when processing changes are made which affect air emissions. Once the permit application is approved, the NJDEPE issues a "Permit to Construct" followed by a "Temporary Certificate to Operate." Temporary Certificates are for 90-day periods and are automatically renewed by the State until the final permit to operate is issued. The final permit is generally issued after a routine inspection by the NJDEPE.

Water discharges are regulated by the New Jersey Department of Environmental Protection and Energy, Division of Water Resources, and the Southeast Morris County Municipal Utilities Authority. Because the SMCMUA wastewater treatment plant operates within the guidelines of the NJDEPE and has been authorized by the State, the Warner-Lambert Industrial Wastewater Discharge permit is issued by the Township of Morris.

The generation and disposal of hazardous wastes are regulated by New Jersey Administrative Code (N.J.A.C.) 7:26 which is an authorized program meeting the requirements of the Federal Resource Conservation and Recovery Act. There is no treatment or long-term storage of hazardous waste on-site. Off-site disposal of hazardous waste is performed in accordance with N.J.A.C. and the state and federal requirements for Hazardous Materials Transportation. The building which includes the Parke-Davis Manufacturing Operations has EPA Identification NJD001344506.

Nonhazardous pharmaceutical and other product or raw material wastes are disposed of by licensed haulers in either nonhazardous or hazardous waste incinerators. Product related waste is not handled by local municipal trash haulers.

Solid Waste Incineration

Resource Conservation and Recovery Act (RCRA) hazardous wastes are disposed of by 1 of 2 hazardous waste haulers.

or

RCRA nonhazardous pharmaceutical wastes from production and the laboratories are destroyed by high temperature (1800°F-2200°F) by:

or

Warner-Lambert certifies that the Morris Plains facility is in substantial compliance within permit limits and environmental regulations.

3.14.4.5. Sites of Product Use

Procanbid 500- and 1000-mg controlled-release tablets are intended for administration in hospitals, clinics, and under home care. Distribution will be nationwide and the drug will be made available through physician offices and hospital and community

pharmacies. With such usage, procainamide hydrochloride and its metabolites would enter municipal sewage treatment systems throughout the United States.

3.14.4.6. Sites of Product Disposal

Returned and unused drug product will be returned via the Warner-Lambert Drug Distribution System. Material with inadequate shelf-life for distribution will be sent to the following facilities:

Warner-Lambert Company
400 W Lincoln Avenue
Lititz, PA 17543

or

[redacted], NJ 07416

Returned products will be destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations.

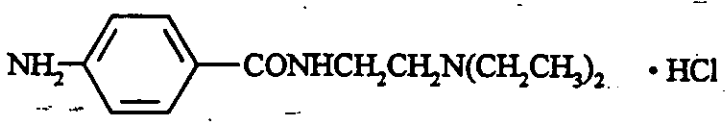
Material that does not meet specifications will be either reprocessed at the manufacturing sites specified and submitted as a supplement to the NDA or destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations.

3.14.5. Identification of Chemical Substances That are the Subject of the Proposed Action

Procainamide hydrochloride (USAN)

3.14.5.1. Nomenclature and Structure

3.14.5.1.1. Structure



3.14.5.1.2. Chemical Name

Benzamide, 4-amino-N-[(2-diethylamino)ethyl]-, monohydrochloride
p-Amino-*N*-[(2-diethylamino)ethyl]benzamide monohydrochloride

3.14.5.1.3. Molecular Formula and Weight

$C_{13}H_{21}N_3O \cdot HCl$ 271.79 (anhydrous monohydrochloride)
235.33 (anhydrous free base)

3.14.5.1.4. Other Names

Procainamide

3.14.5.1.5. CAS Registry Number

CAS 614-39-1

3.14.5.1.6. Laboratory Code Numbers

CI-610 Hydrochloride
PD 18481-2

3.14.5.2. Physical and Chemical Properties

3.14.5.2.1. Description

Procainamide hydrochloride is a white to tan, odorless crystalline powder.

3.14.5.2.2. Melting Range

Differential thermal analysis of procainamide hydrochloride yields a sharp endotherm at 169°C. The melting range is 165.0°C to 169.0°C.

3.14.5.2.3. Dissociation Constants

The dissociation constant of procainamide hydrochloride is $pK_a = 9.24$.

3.14.5.2.4. Ultraviolet Spectrum

The wavelength of maximum absorbance is pH dependent. Both methanolic and ethanolic solutions of procainamide hydrochloride solution have a λ_{max} of 282 nm in 0.1N ammonium hydroxide. Addition of acid to the methanolic solution shifts the maximum to 293 nm.

3.14.5.2.5. Octanol-Water Partition Coefficient (expressed as Log P)

Octanol-water partition coefficients for procainamide hydrochloride were determined using the shake-flask method. The following results were obtained:

Aqueous Phase	Concentration	Log P
0.1 M Phosphate Buffer, pH 7.4	0.05 mg/mL	-1.29 ± 14.8
0.1 M Phosphate Buffer, pH 7.4	0.5 mg/mL	-1.19 ± 1.75
0.05 M Borate Buffer, pH 9.1	0.05 mg/mL	0.54 ± 2.8
0.05 M Borate Buffer, pH 9.1	0.5 mg/mL	0.51 ± 1.1

3.14.5.2.6. Solubility

Procainamide hydrochloride is very soluble in water and both basic and acidic aqueous solutions. It is soluble in 95% ethanol and sparingly soluble in propylene glycol.

3.14.5.2.7. Vapor Pressure

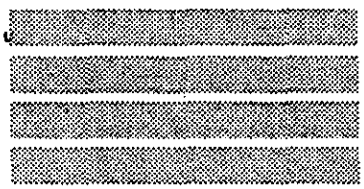
Extensive vapor pressure studies have not been conducted on procainamide hydrochloride. Due to its high melting range the vapor pressure of the drug substance can be expected to be $< 10^{-6}$ torrs.

3.14.5.3. Intermediates and Impurities

The intermediates potentially isolated in the manufacturing of the drug substance are p-nitrobenzoyl chloride (also an alternate starting material) and p-nitro-N(2-diethylaminoethyl)benzamide hydrochloride. No major impurities have been identified in the drug substance. The major potential degradation product has been identified as p-aminobenzoic acid.

3.14.5.4. Substances Used in Manufacturing of Drug Substance

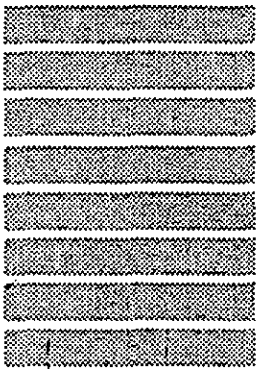
The following substances are used in the manufacturing of procainamide hydrochloride at the Holland, Michigan facility noted in Section 3.14.4.4.1 of this environmental assessment. There are 2 potential routes of synthesis of procainamide hydrochloride described in the NDA and both routes are acceptable for production of drug substance. The materials used are as follows:



Confidential Business Information (CBI)

Reagents, Solvents, and Auxiliary Materials

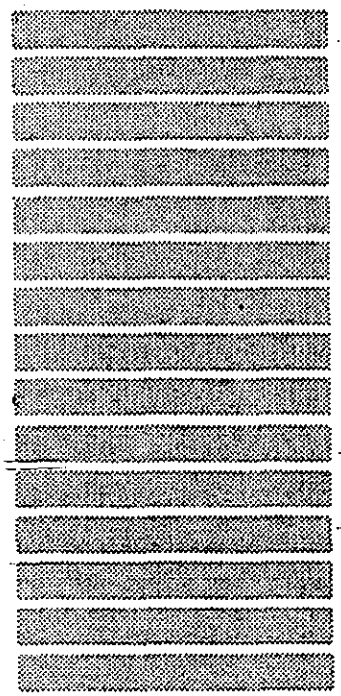
The substances listed below are used in this process and do not become a part of the final chemical molecule.



CBI

3.14.5.5. Substances Used in Manufacturing of Drug Product

The following substances are used in the manufacturing of procainamide hydrochloride controlled-release tablets at the Morris Plains, New Jersey facility noted in Section 3.14.4.4.2 of this environmental assessment.



CBI

[redacted]

3.14.5.6. Metabolites from Administration of Drug Product

Procainamide hydrochloride metabolism has been extensively studied by numerous investigators and reported in the literature.(1) Procainamide hydrochloride is extensively metabolized in humans. Approximately 40% to 60% of the administered drug is excreted in the urine as procainamide with the remaining material excreted as the acetylated metabolite N-acetyl-procainamide (NAPA). Less than 10% of the administered dose has been found to be p-aminobenzoic acid (PABA). A summary of the human pharmacokinetics can be found in *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring*(1), Evans et al, 1992. Since the major metabolite of procainamide (NAPA) is excreted at lower levels than the parent compound, the environmental fate of procainamide hydrochloride was evaluated.

3.14.5.7. Degradation Products of Drug Substance

The primary degradation compound of procainamide hydrochloride has been found to be p-aminobenzoic acid.

3.14.6. Introduction of Substances Into the Environment

3.14.6.1. Substances Emitted From Drug Substance Manufacturing

3.14.6.1.1. Holland Chemical Facility

The materials used in the manufacturing and processing of procainamide hydrochloride are listed in Section 3.14.5.4 of this environmental assessment. Further information on the processing and disposition of these materials is provided in this section.

Air

A description of the process and the controls used to limit emissions of each substance and the assumptions and calculations employed for these emissions are provided in the procainamide hydrochloride air emission permit applications for each step of the manufacturing process referenced earlier. Three air emission permits have been granted for the procainamide hydrochloride manufacturing process. These permit numbers are:

Step 1 Permit 877-84 or optionally, Permit 393-84
Step 2 Permit 551-84

From the air permits, it has been shown that the following maximum emissions from each step of the manufacturing are predicted as follows:

Substance	Maximum Total Annual Emission (lb)
Step 1 Permit 877-84	
Volatile Organic Carbon	
CBI	
Particulate	

Step 1 Permit 393-84 (Optional - Secondary Process)

Volatile Organic Carbon

Particulate

Step 2 Permit 551-84

Volatile Organic Carbon

Particulate

The approval of the proposed action will have no effect upon compliance with current emission standards. All process residuals and emissions are compared with applicable regulatory restrictions as part of the manufacturing development and implementation process. Necessary permits and control devices have been obtained prior to manufacture.

Water

Water is not used in the procainamide hydrochloride manufacturing process and, therefore, there are no direct aqueous wastes. Rinses from the cleaning of manufacturing equipment are sent to the water treatment process which had been previously described and then sent to the deepwell injection process which has been referenced earlier.

Solid

The solid wastes from the procainamide hydrochloride manufacturing process have been identified as [redacted] and [redacted] which are sent off-site for approved landfill. The [redacted] is recovered.

Solvents

Methyl alcohol and isopropyl alcohol from the manufacturing process are recovered and purified by distillation. The purified alcohol is then recycled on-site or sold. Xylene from the process is sent off-site for incineration.

3.14.6.2. Substances Expected to be Emitted From Drug Product Manufacturing

3.14.6.2.1. Morris Plains Drug Product Formulation Facility

The Morris Plains formulation facility utilizes procainamide hydrochloride drug substance and excipients to produce the extended release tablet dosage form. It is the practice of this facility to account for in the final dosage form 100% of the input ingredients. This yield is calculated for each batch in accordance with GMPs. Any discrepancy of this expected yield is resolved prior to release of the batch for distribution.

The substances which may be expected to be emitted into the environment are very small quantities of product dust. This product dust would be assumed to be in the same ratio as its composition in the product formulation.

Product Dust Control

During the various steps of formulation of the drug product dosage form dust is collected through a series of local vacuum system pickups. These sources are connected to collection filters where 95% of the product dust is collected for disposal. Particulate emissions after control are regulated by the air emission permit.

Dust so collected is periodically removed from the unit and destroyed off-site by high temperature (1800°F-2200°F) incineration as a nonregulated pharmaceutical waste. In general, all product residuals are collected in a dry state and are not entering wastewater treatment systems. Prior to any washings, systems and equipment are thoroughly vacuumed to remove dust and only negligible amounts are discharged to sewers.

Wastewater treatment is comprised of a primary and secondary treatment is performed prior to discharge to the Township of Morris sanitary system.

3.14.6.3. Substances Expected to be Emitted Into Environment From Product Use

The substances expected to be emitted into the environment from use of this product are procainamide hydrochloride and N-acetyl-procainamide (NAPA). The metabolites from the other excipients are common materials used in medications throughout the United States and the incremental usage increase from this product is minimal.

The principal route of procainamide hydrochloride entering the environment in any manner is its use and elimination by human patients. The maximum expected emitted concentration (MEEC) value for procainamide hydrochloride is based on the assumption that none of the drug is metabolized and is provided in the following equation. This equation is based on the assumption that [redacted] of procainamide hydrochloride would be manufactured annually as submitted in the air use permit applications.

$$ppm \text{ (in environment)} = lb/year \text{ production} \times 8.9 \times 10^{-9}$$

[redacted] procainamide hydrochloride/year production results in [redacted] ppm. The source of this equation is:

$$ppm = A \times B \times C \times D \times E \times F$$

Where: A = Pounds/year production
B = Year/365 days
C = Day person/130 gal
D = $1/285 \times 10^6$ persons (US population)
E = Gallons/8.34 lb
F = 10^6

3.14.6.4. Substances Expected to be Emitted Into Environment From Product Disposal

Drug substance and tablets that fail specifications, pass expiration period, or are returned from the field are destroyed by high temperature (1800°F-2200°F) incineration by approved and regulated facilities.

3.14.7. Fate of Emitted Substances

3.14.7.1. Fate of Emitted Substances From Drug Substance Manufacture

Air

From the air permit applications, it was seen that quantities of [redacted] may be released by the procainamide hydrochloride manufacturing process. The environmental fates and effects of the approved emissions of [redacted] are found in *Fate and Exposure Data, Solvent Volume II*[2], Howard, et al, 1990. The maximum emissions of [redacted] and [redacted] are estimated at less than [redacted] lb/year and should have no environmental consequence.

Water

Aqueous washings of equipment from the procainamide hydrochloride process are treated by the onsite chemical treatment facility and disposed of by deepwell injection under deepwell injection Permits MI-139-1W-0003, MI-139-1W-0004, and MI-139-1W-0005.

Land

[redacted] and [redacted] are the solid waste by-products from manufacturing of procainamide hydrochloride. These materials would be disposed of by approved landfill. [redacted] is recovered and reused.

3.14.7.2. Fate of Emitted Substances From Drug Product Manufacture

Air

From Section 3.14.6.2, it was seen that the materials that may possibly be released into the atmosphere are small quantities of product dust that bypass the dust collection system. This dust would be subject to rainout and not accumulate in the air compartment. The fate of the active drug substance would be similar to that described in Section 3.14.7.3 for drug product use discharged to aqueous systems.

Water

Product residuals are vacuumed prior to washing and collected as dust. As such, no materials are anticipated in effluents and cleaning of product equipment and processing. Minimal or negligible discharges are anticipated.

Land

The majority of the emitted wastes from procainamide hydrochloride tablet manufacturing is product dust collected as waste materials by the dust collection system. This material is sent off-site for high temperature (1800°F-2200°F) incineration. No material would be expected to enter the environment.

3.14.7.3. Fate of Emitted Substances From Drug Product Use

Air

Material that is inadvertently released into the air compartment would return to earth by rainout.

Water

Based on a solubility of greater than 100 mg/mL, octanol-water partition coefficients of less than zero and an expected vapor pressure of less than 10^{-6} torrs, procainamide hydrochloride would not be expected to accumulate in sludge, ground or atmospheric systems, but remain in aqueous compartments. Based on information provided in the *Environmental Assessment Technical Assistance Handbook,* FDA 1987[3], based on the physical/chemical properties of the drug substance, the primary area of evaluation would be the fate of procainamide hydrochloride in aqueous systems. The majority of the administered dose of procainamide hydrochloride would be released to sanitary sewer systems as procainamide hydrochloride along with the metabolite N-acetyl-procainamide (NAPA). Only the fate of procainamide hydrochloride is discussed. Similar fates would be anticipated for NAPA.

Procainamide hydrochloride drug substance was submitted to a contract laboratory for determining the aerobic biodegradation in aqueous systems in accordance with *FDA Technical Assistance Handbook*[3], Section 3.11. The results of this study determined that procainamide hydrochloride did not significantly degrade under the necessary test conditions. Due to the lack of degradation, the half-life of procainamide hydrochloride in the environment is estimated to be greater than 28 days.

As a result of the outcome of the aerobic biodegradation in water test for procainamide hydrochloride, drug substance was submitted to a contract laboratory to determine the sorption/desorption properties in accordance with *FDA Technical Assistance Handbook*[3], Section 3.08. The results of this study indicated that the procainamide hydrochloride is considered bound to Arkansas silt loam and Kansas sandy loam in 0.01 M $CaCl_2$ and reagent water. It was considered to be moderately

bound to Wisconsin silty clay loam in reagent water and mobile in Wisconsin silty clay loam using hardened water (0.01 M $CaCl_2$).

Summaries of the procaine environmental fate studies are provided in Section 3.14.15.2. Wzielinski May 10, 1995 BGR 5/15/95

3.14.7.4. Fate of Emitted Substances From Drug Product Disposal

As was reported in Section 3.14.4.6, drug substance and drug product which does not meet specifications will be reprocessed and submitted as a supplement to the NDA or disposed of by approved high temperature (1800°F-2200°F) incineration in accordance with all environmental regulations. Returned drug product from the field which passes expiration dating will be destroyed by an approved high temperature (1800°F-2200°F) incinerator.

3.14.8. Environmental Effects of Released Substances

Based on the results of the soil sorption/desorption studies and aerobic biodegradation in water studies for procainamide hydrochloride, drug substance was submitted to a contract laboratory to determine the toxicity of procainamide hydrochloride to daphnids under static conditions in accordance with *FDA Technical Assistance Handbook*[3], Section 4.08. From the results of this study, the 48-hour EC_{50} was [redacted]20 mg of procainamide hydrochloride/liter. The No-Observed-Effect Concentration (NOEC) established for this study was determined to be 13 mg of procainamide hydrochloride/liter. This is many orders of magnitude greater than the calculated MEEC value of [redacted] ppm from Section 3.14.6.3.

Additionally, the drug substance was submitted to a contract laboratory to determine the toxicity of procainamide hydrochloride to microbial populations in accordance with *FDA Technical Assistance Handbook*[3], Section 4.02. The study determined that the Minimum Inhibitory Concentration (MIC) for *Aspergillus niger, Trichoderma viride, Clostridium perfringens, Bacillus subtilis*, and *Nostoc sp.* was greater than 1000 mg/L (1 mg/mL) for all species tested. Again, this is many orders of magnitude greater than the calculated MEEC value of [redacted] ppm calculated in Section 3.14.6.3.

Summaries of the procainamide hydrochloride environmental effect studies are provided in Section 3.14.15.3.

The effects on the environment from the drug substance manufacturing, drug product manufacturing, drug use, and drug disposal will be minimal. From the chemical information provided, spills, accidental releases, and minor emissions will confine the drug substance to aqueous compartments where a lack of toxic effects to daphnia and microbial populations has been demonstrated at levels well above the expected MEEC values.

3.14.9. Use of Resources and Energy

The proposed action does not require a large increase of resources and energy above current operating levels at the existing facilities. The increase in activity at the listed manufacturing sites is estimated as less than 2.0% of existing levels. No impact upon existing permit levels is anticipated at this level of increase. No new material usage is anticipated with this action. There is no threat to endangered species and the facilities are not located on historic sites.

3.14.10. Mitigation Measures

Since no adverse events or consequences are foreseen with this proposed action, no further mitigation measures are proposed or anticipated.

3.14.11. Alternatives to the Proposed Action

1. No action
2. Provide patients with cardiac arrhythmias a more convenient dosage regimen for this condition

3.14.12. List of Preparers

Sean T. Brennan, PhD
Worldwide Regulatory Affairs

Alexander J. Brankiewicz, BSChE
Worldwide Regulatory Affairs

3.14.13. Certification

The undersigned officials certify to the best of their knowledge that the information presented is true, accurate, and complete for preparation of the environmental assessment.

Sean Brennan 12/9/94

(Signature of Responsible Official) (Date)

(Name) Sean T. Brennan, PhD

(Title) Senior Director
Worldwide Regulatory Affairs
Parke-Davis Pharmaceutical Research

Alexander J. Brankiewicz 12/8/94

(Signature of Responsible Official) (Date)

(Name) Alexander J. Brankiewicz, BSChE

(Title) Manager
Worldwide Regulatory Affairs
Parke-Davis Pharmaceutical Research

3.14.14. List of References

1. Evans, et al. Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring. Vancouver, Washington: Applied Therapeutics Inc, 1992.

2. Howard PH, ed. Handbook of environmental fate and exposure data for organic chemicals, Volume II. Chelsea, Michigan: Lewis Publishers, Inc, 1990.

3. Food and Drug Administration. Environmental assessment technical assistance handbook. Washington, DC: NTIS, 1987.

4. Florey K, ed. Analytical Profiles of Drug Substances 1975;4:333-381.

3.14.15. Summary Tables

3.14.15.1. Summary Tables of Physical-Chemical Properties

Procainamide Hydrochloride

Nomenclature and Structure

Structure

Chemical Name

p-Amino-*N*-[(2-diethylamino)ethyl]benzamide monohydrochloride
Benzamide, 4-amino-*N*-[(2-diethylamino)ethyl]-, monohydrochloride

Molecular Formula and Weight

$C_{13}H_{21}N_3O \cdot HCl$ 271.79 (anhydrous monohydrochloride)
235.33 (anhydrous free base)

Other Names

Procainamide

CAS Registry Number

CAS 614-39-1

Laboratory Code Numbers

CI-610 Hydrochloride
PD 18481-2

Physical and Chemical Properties

Description

Procainamide hydrochloride is a white to tan, odorless crystalline powder.

Melting Range

Differential thermal analysis of procainamide hydrochloride yields a sharp endotherm at 169°C. The melting range is 165.0°C to 169.0°C.[4]

Dissociation Constants

The dissociation constant of procainamide hydrochloride is $pK_a = 9.24$.[4]

Ultraviolet Spectrum

The wavelength of maximum absorbance is pH dependent. Both methanolic and ethanolic solutions of procainamide hydrochloride solution have a λ_{max} of 282 nm in 0.1N ammonium hydroxide. Addition of acid to the methanolic solution shifts the maximum to 293 nm.[4]

Octanol-Water Partition Coefficient (expressed as Log P)

Octanol-water partition coefficients for procainamide hydrochloride were determined using the shake-flask method. The following results were obtained:

Aqueous Phase	Concentration	Log P
0.1 M Phosphate Buffer, pH 7.4	0.05 mg/mL	-1.29 ± 14.8
0.1 M Phosphate Buffer, pH 7.4	0.5 mg/mL	-1.19 ± 1.75
0.05 M Borate Buffer, pH 9.1	0.05 mg/mL	0.54 ± 2.8
0.05 M Borate Buffer, pH 9.1	0.5 mg/mL	0.51 ± 1.1

Solubility

Procainamide hydrochloride is very soluble in water and both basic and acidic aqueous solutions. It is soluble in 95% ethanol and sparingly soluble in propylene glycol.[4]

Vapor Pressure

Extensive vapor pressure studies have not been conducted on procainamide hydrochloride. Due to its high melting range the vapor pressure of the drug substance can be expected to be $<10^{-6}$ torrs.

3.14.15.2. Summary of Environmental Fate Studies

3.14.15.2.1. Summary of Procainamide Hydrochloride Aerobic Biodegradation in Water Study

Sponsor: Parke-Davis, Warner-Lambert

Protocol Title: Test Article: Determination of Aerobic Biodegradation in Water Using Unlabeled Test Article, Following FDA Technical Assistance Handbook, Document §3-11, [redacted] FDA 3.11 UNL./Parke and Protocol Amendment 1, dated June 22, 1994

Report Number:	94-10-5509
Study Number:	10320.0494.6150.725
Test Article:	Procainamide hydrochloride (CI-610), Lot H746573 8/W, reported by the Study Sponsor to have a purity of 100.4%, was received from Warner-Lambert, Ann Arbor, Michigan, on April 6, 1994.
Experimental Test Dates:	Acclimation: June 22 to July 7, 1994 Biodegradation: July 8 to August 5, 1994
Procedures Followed:	The carbon dioxide evolution method was followed. This study was conducted for 28 days with procainamide hydrochloride and the reference material, sodium benzoate. Chemical-specific high-performance liquid chromatography (HPLC) analysis was used to monitor primary biodegradation.
Results:	On Day 28, the last day on which HPLC analysis was conducted, concentrations of procainamide hydrochloride were 18.8 to 20.8 mg/L, an average of 98.3% of mean Day 0 concentration. TOC analysis also indicated no net loss of test article from solution, although CO_2 evolution averaged 29% of nominal.

Conclusion:	Limited evidence for biodegradability of procainamide hydrochloride was obtained in this test; the apparent CO_2 production from the test article is more likely due to microbial stimulation. Based upon the HPLC and TOC data, procainamide hydrochloride has a half-life greater than 28 days when exposed to an acclimated, aerobic microbial community.

3.14.15.2.2. Summary of Procainamide Hydrochloride Soil Sorption/Desorption Study

Sponsor:	Parke-Davis, Warner-Lambert Company
Protocol Title:	"Test Article: Determination of Sorption and Desorption Properties Following the FDA Technical Assistance Handbook Section #3.08.", [redacted]/FDA 3.08/Parke and Protocol Amendment 1, dated June 10, 1994
Report Number:	94-10-5505
Study Number:	10320.0494.6149.710
Test Material:	Procainamide hydrochloride (CI-610), Lot H746573 8/W, CAS Registry 614-39-1, a white to off-white solid, reported by the Study Sponsor to have a purity of 100.4%, was received from Warner-Lambert on April 6, 1994.
Experimental Test Dates:	June 14 to July 28, 1994

Results:

A screening test determined that sorption was 25.7% and desorption was greater than 75% with the Wisconsin silty clay loam in 0.01 M $CaCl_2$, precluding the need for further testing with this soil in this matrix (US FDA, 1987a). The mean sorption distribution coefficient, K_d, and organic carbon sorption coefficient, K_{oc}, determined in that screening test were 1.73 and 54.6, respectively.

Advanced isotherm testing was conducted with 0.01 M $CaCl_2$ in Arkansas silt loam and Kansas sandy loam and with reagent water in Arkansas silt loam, Kansas sandy loam and Wisconsin silty clay loam. The mean K_{oc} value in 0.01 M $CaCl_2$ was determined to be 2,820 for the Arkansas soil and 2,480 in the Kansas soil. In reagent water, the mean K_{oc} value was determined to be 24,200 for the Arkansas soil, 117,000 in the Kansas soil and 771 in the Wisconsin soil.

Conclusions:

Based on the results of this study, procainamide-hydrochloride is considered to be tightly bound to the Arkansas and Kansas soil in 0.01 M $CaCl_2$ and reagent water. Procainamide hydrochloride was considered to be moderately bound to the Wisconsin soil in reagent water and mobile in Wisconsin soil using hardened water (0.01 M $CaCl_2$).

3.14.15.3. Summary of Environmental Effects Studies

3.14.15.3.1. Summary of Procainamide Hydrochloride Acute Toxicity to Daphnia Magna Study

Procainamide Hydrochloride - Acute Toxicity
to Daphnids (*Daphnia magna*) Under Static Conditions

Sponsor:	Parke-Davis, Warner-Lambert
Protocol Title:	"Test Article: Static Acute Toxicity Test With *Daphnia magna* Following the FDA Environmental Assessment Technical Assistance Handbook, §4.08," [redacted] FDA 4.08/DM-SA/ PARKE and Protocol Amendment 1, dated June 13, 1994.
Report Number:	94-8-5417
Study Number:	10320.0494.6152.110
Test Article:	Procainamide Hydrochloride, CI-610, Lot H746573 8/W, CAS Registry 614-39-1, a white to off-white solid, reported by the Study Sponsor to have a purity of 100.4%
Test Dates:	June 14 to 16, 1994

Procainamide BID Tablets	34	
Species:	*Daphnia magna* Age: ≤24 hours Source: [redacted] culture facility	
Dilution Water:	Fortified well water pH: 8.1 Specific Conductivity: 500 µmhos/cm Total Hardness as $CaCo_2$: 180 mg/L Total Alkalinity as $CaCO_3$: 120 mg/L	
Test Temperature:	22°C	
Nominal Test Concentrations:	13, 22, 37, 60, and 100 mg AI/L	
Mean Measured Test Concentrations:	13, 22, 39, 61, and 100 mg AI/L	
Results:	The 48-hour EC_{50} value was calculated by binomial probability/nonlinear interpolation to be 20 mg AI/L (95% confidence interval of 13-39 mg AI/L). The No-Observed-Effect Concentration (NOEC) was determined to be 13 mg AI/L. The EC_{50} and the NOEC can also be expressed in terms of the concentration of the free base and are reported as 17 and 11 mg/L, respectively.	

3.14.15.3.2. Summary of Procainamide Hydrochloride Microbial Growth Inhibition Study

Procainamide Hydrochloride (CI-610) -
Determination of Microbial Growth Inhibition

Study Sponsor:	Parke-Davis, Warner-Lambert Company
Protocol Title:	"Test Article: Determination of Microbial Growth Inhibition Following FDA Technical Assistance Handbook, Document §4.02," [redacted] FDA 4.02/Parke and Protocol Amendment 1, dated May 4, 1994.
Report Number:	94-5-5284
Study Number:	10320.0494.6151.770
Test Article:	Procainamide hydrochloride (CI-610), Lot H746573 8/W, white crystal, 100.4% pure, received April 6, 1994
Test Dates:	April 27 to May 11, 1994
Species:	*Aspergillus niger, Trichoderma viride, Clostridium perfringens, Bacillus subtilis*, and *Nostoc sp.*
Test Concentrations:	0.10, 1.0, 10, 100, and 1000 mg/L

Results:

Species	CI-610 MIC (mg/L)	
	Expressed as Salt Form	Expressed as Free Base
Aspergillus niger	>1000	>866
Trichoderma viride	>1000	>866
Clostridium perfringens	>1000	>866
Bacillus subtilis	>1000	>866
Nostoc sp.	>1000	>866

Attachment 7

Curriculae Vitae for Environmental Assessment Preparers

CURRICULUM VITAE

Sean T. Brennan, PhD

Address: 1236 Ardmoor Ave
Ann Arbor, MI 48103
(313) 663-2832

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105-1047
(313) 996-7596

Education

1982	PhD, University of Iowa, Iowa City, IA, Analytical Chemistry
1979	MS, University of Iowa, Iowa City, IA, Analytical Chemistry
1977	BS, DePaul University, Chicago, IL, Chemistry

Professional Experience

April 1993 - Present — Senior Director, Worldwide Regulatory Affairs, Parke-Davis

Chemistry, Manufacturing and Controls sections of regulatory applications and Drug Master Files on a worldwide basis for new and marketed products

Liaison with FDA on CMC issues

Provide technical regulatory guidance to R&D and Manufacturing

Regulatory Affairs for Warner-Chilcott (generic drug business unit within Parke-Davis)

	CMC Audit function for applications, supplements and annual reports
	Manage group of six manger/sr. managers, six regulatory associates, five auditors, and four administrative assistants
February 1992 - April 1993	Director, Worldwide Regulatory Affairs
October 1989 - February 1992	Associate Director, Worldwide Regulatory Affairs Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan
Responsibilities:	Review and coordinate preparation of Chemistry, Manufacturing, and Controls section of regulatory applications on a worldwide basis
	Respond to Regulatory Agencies inquiries on pending applications and meet with Agency personnel as necessary
	Provide technical regulatory guidance to development and manufacturing groups
	Manage group of two senior managers, three managers, and two senior regulatory affairs associates
July 1989 - October 1989	Senior Research Associate, Chemical Development, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan
October 1987 - July 1989	Research Associate, Chemical Development, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan
March 1984 - October 1987	Senior Scientist, Chemistry Department, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan
Responsibilities: (for the above positions)	Develop and validate chromatographic methods (HPLC, TLC, and GLC) for the analysis of drug substances, intermediates, drug-diet admixtures, solutions/suspensions, and dosage forms

Prepare Chemistry, Manufacturing, and Controls section for drug substances for INDs and NDAs and responding to FDA questions and comments

Design and conduct drug substance stability studies

Isolate and identify process impurities and drug substance degradation products

Supervise one PhD, two MS level, and one BS level chemists

October 1982 - March 1984 — Scientist, Chemistry Department, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan

Responsibilities:

Develop and validate analytical methods to determine the elemental composition and pharmaceutically active compounds

Supervise the elemental microanalysis laboratory (two technicians)

Prepare Chemistry, Manufacturing, and Controls section for drug substances for INDs and NDAs and respond to FDA questions and comments

Certify drug substances for toxicological and clinical use

September 1977 - University of Iowa, Chemistry Department, Iowa City, Iowa Teaching/Research Fellowship; Research includes the study of the effects of temperature and humidity on urea-formaldehyde foam insulation and development evaluation of novel methods for the determination of nitrite, nitrate, and N-nitrosamines. Instrumental experience in atomic absorption spectrometry, gas chromatography, liquid chromatography, scanning electron microanalysis, and x-ray fluorescence.

Publications

1. Emission of Formaldehyde from Urea-Formaldehyde Polymers, Master's Thesis, University of Iowa, 1979. C. W. Frank, PhD, Supervisor.

2. Problems Associated with the Use of Urea-Formaldehyde Foam for Residential Insulation, Part I; The Effects of Temperature and Humidity on Formaldehyde Release from Urea-Formaldehyde Foam Insulation, K. R. Long, S. T. Brennan, D. A. Pierson, and C. W. Frank, National Technical Information Service, ORNL/SUB-7559/I, September 1979.

3. Development of Rapid and Sensitive Methods for the Trace Level Determination of Nitrate, Nitrite, and N-Nitroso Group Content, PhD Dissertation, C. W. Frank, PhD, Supervisor.

4. Rapid Determination of N-diethanolnitrosamine in Cosmetics, J of the Society of Cosmetic Chemists, January/February 1983.

CURRICULUM VITAE

Alexander J. Brankiewicz

Address:

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Southfield, Michigan 48076
(810) 557-3852

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48105-1047
(313) 996-1399

Education:

1975	BSChE, University of Michigan, Ann Arbor, Michigan (Chemical Engineering)

Professional Experience:

May 1992-Present	Manager, Worldwide Regulatory Affairs, Parke-Davis
Responsibilities	Prepare Chemistry, Manufacturing and Controls sections of regulatory applications and Drug Master Files on a worldwide basis for new and marketed products
	Interact with FDA on CMC issues
	Provide technical regulatory guidance to Research and Development and Manufacturing
May 1990-May 1992	Senior Regulatory Associate, Worldwide Regulatory Affairs
	Prepare Chemistry, Manufacturing and Controls sections of INDs and NDAs

August 1985-May 1990	Project Scientist, Sterile Products, Parke-Davis
Responsibilities	Trouble-shoot and investigate deviations in the manufacturing of sterile drug products
	Develop manufacturing methods and scale-up developmental and third party products
	Develop, qualify and validate automated inspection equipment for the Sterile Operations Facility
	Develop and optimize freeze dryer cycles for lyophilized products
	Technical responsibility for the development and maintenance of biological products
	Supervise the manufacture of developmental products and clinical supplies
January 1976 - August 1985	Assistant Scientist - Senior Associate Scientist, Parke-Davis Research Division
	Pilot plant engineer for the large scale fermentation, purification and isolation of novel microbial products
	Laboratory optimization and process development for purification of novel microbial products
	Perform laboratory analytical methods: HPLC, TLC, enzyme assays, etc. for evaluation of developmental isolation processes
	Investigate and determine structures of novel microbial products by reviewing results of IR, NMR, Mass Spectra, elemental analysis and degradation studies
June 1975 - December 1985	Technical Assistant, University of Michigan
Responsibilities	Operate internal combustion engine dynamometers and analyze and quantitate sulfur compound emissions via gas chromatography and wet chemistry methods (EPA contract)

APPENDIX 4

Letter of Compliance for Holland and Morris Plains Facilities

Warner-Lambert Company
182 Tabor Road
Morris Plains New Jersey 07950
201 540-4355
Fax 201 540-5316

James C. Lime
Vice President
Environmental Affairs & Compliance

WARNER LAMBERT

November 22, 1994

This is to certify that Warner-Lambert's facilities located in Holland, MI and Morris Plains, NJ are in substantial compliance with all applicable federal, state and local environmental laws and regulations.

This is submitted in partial fulfillment of Food and Drug Administration requirements concerning the NDA submission for Procainamide BID.

Sincerely,

James C. Lime

APPENDIX 13

Procainamide Hydrochloride Material Safety Data Sheet

Units per package size: 200 mg

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

address:
12601 Twinbrook Parkway
Rockville, MD 20852 USA

emergency and information
telephone calls:
(301) 881-0666

Jerome A. Halperin — 06-05-90
Responsible Party — date prepared

WARNING STATEMENT

WARNING! REFERENCE STANDARD; NOT FOR HUMAN CONSUMPTION; AVOID INGESTION, INHALATION, SKIN CONTACT. FOR CHEMICAL TEST AND ASSAY USE ONLY.

SECTION 1 - IDENTITY

COMMON NAME	Procainamide Hydrochloride
SYNONYMS	n/a
CAS NUMBER	614-39-1 (hydrochloride); 51-06-9 (procainamide)
RTECS NUMBER	CV2295000 (hydrochloride); CV2275000 (procainamide)
CHEMICAL NAME	Benzamide, 4-amino-N-[2-(diethylamino)ethyl]-, monohydrochloride
.ICAL FAMILY	Aromatic carboxamide
THERAPEUTIC CATEGORY	Antiarrhythmic
FORMULA	$C_{13}H_{21}N_3O.HCl$

SECTION 2 - HAZARDOUS INGREDIENTS

	NAME	PERCENT	THRESHOLD LIMIT VALUE (UNITS)
PRINCIPAL HAZARDOUS COMPONENT(S)/[Chemical & Common name(s)]	Procainamide Hydrochloride	Pure Material	Not Established

SECTION 3 - PHYSICAL AND CHEMICAL CHARACTERISTICS (Fire & Explosion Data)

BOILING POINT	n/a
SPECIFIC GRAVITY (H_2O = 1)	n/a
VAPOR PRESSURE (mm Hg)	n/a
PERCENT VOLATILE BY VOLUME (%)	n/a
VAPOR DENSITY (AIR = 1)	n/a
EVAPORATION RATE	n/a
SOLUBILITY IN WATER	Very soluble

= not applicable

= not applicable

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Procainamide Hydrochloride
Common Name
Cat # 56350

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

LD_{50}: 290 mg/Kg intraperitoneal-mouse;
LD_{50}: 800 mg/Kg subcutaneous-mouse;
LD_{50}: 94640 micrograms/Kg intravenous-mouse;
LD_{50}: 860 mg/Kg intramuscular-mouse]
[Procainamide CAS RN: 51-06-9
TDLo: 8579 mg/Kg/43W-I oral-man;
TDLo: 29 mg/Kg oral-man;
TDLo: 1826 mg/Kg/13W-I oral-woman;
TDLo: 2280 mg/Kg/22W oral-human;
TDLo: 583 mg/Kg/12D-C intravenous-man;
LD_{50}: 1950 mg/Kg oral-rat;
LD_{50}: 110 mg/Kg intravenous-rat;
LD_{50}: 525 mg/Kg oral-mouse;
LD_{50}: 178 mg/Kg intraperitoneal-mouse;
LD_{50}: 720 mg/Kg subcutaneous-mouse;
LD_{50}: 49 mg/Kg intravenous-mouse;
LDLo: 2210 mg/Kg oral-dog;
LD_{50}: 250 mg/Kg intravenous-rabbit;
LD_{50}: 280 mg/Kg intravenous-guinea pig]

ACUTE — Possible allergic reaction to dust if inhaled, ingested or in contact with skin.

CHRONIC — Eye, skin and/or respiratory tract irritation

PRECAUTIONS TO CONSIDER — Possible hypersensitization

Persons developing hypersensitivity (anaphylactic) reactions must receive immediate medical attention. Material may be irritating to mucous membranes and respiratory tract. As a general rule, when handling USP Reference Standards avoid all contact and inhalation of dust, fumes, mists, and/or vapors associated with the material. Keep container tightly closed and use with adequate ventilation; wash thoroughly after handling. Individuals working with chemicals should consider all chemicals to be potentially hazardous even if their individual hazards may be uncharacterized or unknown. Individuals hypersensitive to procaine or other related agents may be hypersensitive to procainamide also. Procainamide crosses the placenta. However, problems in humans have not been documented [USP DI, 10th Ed].

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE	Hypersensitivity to material		
CHEMICAL LISTED AS CARCINOGEN OR POTENTIAL CARCINOGEN	NATIONAL TOXICOLOGY PROGRAM	( ) Yes	(X) No
	I.A.R.C. Monographs	( ) Yes	(X) No
	OSHA	( ) Yes	(X) No

= not applicable

Procainamide Hydrochloride
Common Name
Cat # 56350

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

	ACGIH TLV: n/a		OTHER EXPOSURE LIMIT(S) USED: n/a

OSHA PERMISSIBLE EXPOSURE LIMIT:	Not established
OTHER EXPOSURE LIMIT USED	Not established
EMERGENCY AND FIRST AID PROCEDURES	Remove from exposure. Remove contaminated clothing. Persons developing serious hypersensitivity reactions must receive immediate medical attention. Upon eye or skin contact, flush affected area with copious quantities of water. Obtain medical attention. Treatment of overdose is primarily symptomatic and supportive. Gastric lavage, emesis, hemodialysis, pressor medication and maintenance of airway are of possible benefit according to individuals condition.
1. INHALATION	May cause irritation of respiratory tract. Avoid inhalation. Remove to fresh air.
2. EYES	May cause irritation. Flush with copious quantities of water.
SKIN	May cause irritation. Flush with copious quantities of water.
4. INGESTION	May cause irritation. Flush out mouth with water.

SECTION 6 - SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (SPECIFY TYPE)	Approved dust respirator
VENTILATION	Adequate
LOCAL EXHAUST	Recommended
MECHANICAL (GENERAL)	Recommended
OTHER	n/a
PROTECTIVE GLOVES	Rubber
EYE PROTECTION	Safety goggles
OTHER PROTECTIVE CLOTHING OR EQUIPMENT	Appropriate laboratory apparel

SECTION 7 - SPECIAL PRECAUTIONS AND SPILL/LEAK PROCEDURES

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE	Store in tight container as defined in the United States Pharmacopeia. This material should be handled and stored per label and other instructions to ensure product integrity.

= not applicable

Procainamide Hydrochloride
Common Name
Cat # 56350

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

OTHER PRECAUTIONS	Avoid contact with eyes, skin or clothing. Avoid breathing dust or mist. Use with adequate dust control. Wash thoroughly after handling. Wear fresh clothing daily. Wash contaminated clothing before reuse. Do not permit eating, drinking or smoking near material.
STEPS TO BE TAKEN IN CASE MATERIAL IS SPILLED OR RELEASED	Wear approved respirator and chemically compatible gloves. Vacuum or sweep up spillage. Avoid dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area and wash spill site.
WASTE DISPOSAL METHODS	Dispose of waste in accordance with all applicable Federal, State and local laws.

NOTICE: The information contained herein is applicable solely to the chemical substance when used as a USP Reference Standard and does not relate to any other use of the substance described. Its use is intended by persons having technical skill and at their own discretion and risk. The information has been developed by USP staff from sources considered reliable but has not been independently verified by the USP. Therefore, the USP Convention cannot guarantee the accuracy of the information in these sources nor should the statements contained herein be considered an official expression. NO REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE is made with respect to the information contained herein.

ATTENTION:

This Product is Sold as a Reference Standard for Use In Chemical Analysis Not For Human Consumption.

⌒ = not applicable