ENVIRONMENTAL IMPACT ANALYSIS

Environmental Impact Analysis Report

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

Environmental Assessment - Aredia™ Vials and Ampuls

1. Date — December 15, 1989

2. Name of Applicant — CIBA-GEIGY Corporation

3. Address — Pharmaceuticals Division
556 Morris Avenue
Summit, New Jersey 07901

4. Description of the Proposed Action

A. Requested Action

CIBA-GEIGY has filed a New Drug Application for Aredia™ Vials and Ampuls containing the drug substance pamidronate disodium. Aredia™ is available as 15 mg/5 mL lyophilized vials and 5 mg/5 mL solution ampuls. The New Drug Application requests approval of the use of pamidronate disodium for the treatment of hypercalcemia associated with malignancy.

B. Need for Action

Approval of this Application will result in the production and distribution of Aredia™ Vials and Ampuls in the United States. Approval will offer patients in the United States effective therapy for hypercalcemia associated with malignancy. Because of the therapeutic benefits associated with its availability and use, approval is justified and preferable to non-approval. As pharmaceutical dosing levels are inherently low, quantities of drug product to be manufactured present low environmental risk. Therefore, approval is also justified for environmental reasons.

C. Sites of Production and Environmental Settings

Bulk drug substance will be manufactured at CIBA-GEIGY facilities in Basel - Klybeck and Schweizerhalle, Switzerland.

Drug product formulation will occur at the CIBA-GEIGY facility in Stein, Switzerland. Packaging, consisting of labeling and cartoning operations, will take place at CIBA-GEIGY facilities in Suffern, New York, Summit, New Jersey or at contractor facilities.

The environmental settings of these plants are:

1) Basle, Canton of Basel-Stadt, Switzerland

The CIBA-GEIGY Pharma Chemical production facility is located within the Klybeck site (100 acres) of CIBA-GEIGY Ltd. works in the City of Basle (population 180,000), at the northern end of the urban industrialized area of the town, close to the borders of the Federal Republic of Germany and France. The agglomeration Basle, situated in Switzerland, France and Germany, has a population of approximately 500,000 people. The site is partly adjacent to the Rhine River; the small Wiese River divides the area. The surrounding neighborhood includes, among others, a food processing plant, transportation, printing and retail businesses as well as a large number of dwellings. In Basle, CIBA-GEIGY occupies an area of approximately 130 acres. Totally, over 11,000 people are employed.

Air Resources - Air quality in this area is in compliance with cantonal and federal standards set for sulfur oxides, nitrous oxides and ozone.

Water Resources - Potable water is supplied by the City of Basle. Non-potable water is drawn from the Rhine River by filtration. Storm water drainage and sanitary waste water are discharged to the City of Basle Sewage Treatment plant and then to the Rhine River. The waste water streams stemming from chemical production are separated into polluted and non-polluted (cooling water) waste water. The non-polluted water is discharged into the Rhine River, the polluted water goes to a Chemical Waste Water Treatment plant; finally it is discharged into the Rhine River.

Land Resources - The Klybeck site, of a level terrain, lies over essentially sedimentary type formations. It is fully developed, being covered by buildings, roadways and railroads; it is sparingly landscaped.

2) Schweizerhalle, Canton of Basel-Landschaft, Switzerland

The CIBA-GEIGY Pharma Chemical Production facility is located within the "CIBA-GEIGY Werke Schweizerhalle AG" site situated in the industrialized zone of Schweizerhalle, approximately 5 miles east of the City of Basle, adjacent to the Rhine River which is also the boundary to the Federal Republic of Germany. CIBA-GEIGY works Schweizerhalle occupy an area of approximately 52 acres; totally, approximately 2,250 people are employed. The surrounding neighborhood consists mainly of chemical industry.

Air Resources - Air quality in this area is in compliance with cantonal and federal standards set for sulfur oxides, nitrous oxides and ozone.

Water Resources - Potable water is supplied by the public Hardwasser AG. Non-potable water is drawn from wells within the works (Rhine water). The waste water streams stemming from chemical production are separated into polluted and non-polluted (cooling water) waste water. The non-polluted water is discharged into the Rhine River. The polluted water, after an on-site pretreatment (if necessary), as well as sanitary waste water and storm water drainage goes to the "ARA Rhein", a sewage treatment plant jointly used by the public and the industry; finally it is discharged into the Rhine River.

Land Resources - The Schweizerhalle site, a level terrain, lies over essentially sedimentary type formations. It is fully developed, being covered by buildings, roadways and railroads.

3) Stein, Canton of Aargau, Switzerland

The CIBA-GEIGY Pharma site at Stein consists of the Pharmaceutical (drug product) Production facilities and a Pharma Chemical Production milling plant. The Stein site is situated on a 135 acres area, approximately 20 miles east of the City of Basle, adjacent to the Rhine River which is also the boundary to the Federal Republic of Germany. Totally, approximately 1,200 people are employed. The surrounding neighborhood consists mainly of farm land, the Village of Stein and, across the Rhine River, the resort town of Bad Saeckingen (Federal Republic of Germany).

Air Resources - Air quality in this area is in compliance with cantonal and federal standards set for sulfur oxides, nitrous oxides and ozone.

Water Resources - Potable water is obtained from the Village of Stein water supply, originating from wells located close to the Stein site. Cooling water, originating from wells on the site, is of the same quality as the public water supply. Cooling water and storm water drainage is discharged into the Rhine River. Polluted water as well as sanitary water goes to the Joint Sewage Treatment Plant of Stein and Bad Saeckingen; finally it is discharged into the Rhine River.

Land Resources - The Stein site, of a level terrain, lies over essentially sedimentary type formations. Only a minor part of it is developed, being covered with buildings, roadways and parking lots, and with landscaped areas. The remainder of the property is farm land.

4) Summit, New Jersey - This CIBA-GEIGY Pharmaceutical Division facility is located on approximately 92 acres of land in the City of Summit (pop. 25,000), Union County, New Jersey, approximately 30 miles southwest of New York City. The site consists of fifty buildings covering over 1.3 million square feet and employs an average work force of 1900 people. It is adjacent to the Passaic River, a source of potable water. The surrounding neighborhood includes retail businesses, light industry and private residences.

Air Resources - Air quality in this area is in compliance with the standards set for suspended particulates, nitrous oxides and sulfur oxides. The entire state of New Jersey is in non-compliance with the National Ambient Air Quality Standard for Ozone.

Water Resources - The Summit facility draws its potable water from six on-site wells as well as a public water supplier (Commonwealth Water Co.). Storm water drainage is achieved by a series of catchbasins connected to a piping system which ultimately discharges to the Passaic River regulated by New Jersey Pollutant Discharge Elimination System (NJPDES) Permit #NJ0000540. There is waste water pretreatment on-site consisting of equalization and neutralization with all process and sanitary waste water being discharged into a Publicly Owned Treatment Works, the Joint Meeting, located in Elizabeth, New Jersey, which discharges into the Arthur Kill. This is also regulated by a NJPDES permit.

Land Resources - The 92 acre site lies over essentially sedimentary type formations. The majority of the site, which is of a level terrain, is developed, being covered by buildings, roadways and parking lots, with landscaped areas. The remainder of the property is undeveloped wooded area.

5) Suffern, New York - This CIBA-GEIGY pharmaceutical manufacturing facility is located in Suffern, New York on a 162 acre site approximately 30 miles northwest of New York City. The site is bounded by the New York State Thruway on the north, Hemion Road on the east, the Conrail Piermont Line on the south and the Plaza Material Corp. quarry on the west. The surrounding neighborhood includes retail businesses, light industry and private residences.

Air Resources - The air quality in the region meets the ambient air quality standards established by the State of New York for sulfur dioxide, suspended particulates, carbon monoxide, photochemical oxidants, hydrocarbons, nitrogen oxides, hydrogen sulfide and beryllium. The standard for ozone is not met.

Water Resources - Potable water is obtained from the Village of Suffern water supply, originating in wells located within the village. There are no non-potable sources or systems. Sanitary and process waste water flows into the Village of Suffern sewer system and is treated by the municipal plant before discharge into the Ramapo River., This CIBA-GEIGY permit is not numbered.

Storm water is directed off the site by a separate system into an unnamed stream which ultimately discharges into the Ramapo River.

Land Resources - The developed portion of the site, approximately 33 acres, is generally flat, at an average elevation of approximately 310 feet above sea level.

The nature of the soil is characterized as glacial deposits, consisting of sand, gravel and a till mixture of sand, gravel, boulders and clay, with sandstone and shale bedrock.

The principal buildings on the site are the Manufacturing Building, the Development Building and the Boiler House, with minor construction consisting of two storage buildings, a fire pump house and a sewage pump house.

6) Contract Operations

Descriptions of the environmental settings of these facilities should be found in their Drug Master Files.

D. Sites of Product Use

Aredia™ Vials and Ampuls are intended for use throughout the United States as a hypercalcemia medication for human intravenous infusion.

E. Sites of Product Disposal

Air Emissions - All rejected or returned products are incinerated off site at either

The expected emissions from the burning of the wastes are water vapor, carbon dioxide and small quantities of nitrous oxides.

Aqueous Emissions - Waste water from pollution control equipment associated with the incineration of discarded materials will be generated. This water is treated by the facilities before discharge in accordance with their operating permits.

Solids Emissions - Where possible, discarded packaging components are sold to a reclaimer/recycler. The incineration of the returned and rejected materials generates residual solids which are disposed of by the solid disposal sites in accordance with their operating permits

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

Information concerning the chemical name, empirical formula, molecular weight, and chemical structure of pamidronate disodium can be found in Appendix I, Parts I and II.

6. Introduction of Substances into the Environment

A. Substances to be Emitted

1) Bulk Chemical Production - Appendix II, Part I summarizes data describing substances which may be expected to be emitted to the environment during the production of the drug substance.

2) Drug Product Formulation - Appendix II, Part II summarizes data describing substances which may be expected to be emitted to the environment during the production of the Aredia™ Vials and Ampuls.

B. Controls in Effect

1) Controls

a) Basle, Canton of Basel-Stadt, Switzerland

Air Controls - Air emissions stemming from the synthesis of bulk drug substances are controlled by equipment such as surface condensers, brine-cooled vent condensers (-15°C) and scrubber systems operating with either plain water or acidic, basic or oxidizing aqueous solutions. Air emissions from the on-site incinerator are controlled by a series of scrubbers operating with aqueous absorption mediums. The equipment is in compliance with permits of the Construction Supervision Department of the Canton of Basel-Stadt (= Bauinspektorat des Kantons Basel-Stadt) and the Department of Air Pollution Control (= Kantonales Lufthygieneamt).

Liquid Controls - All waste solvents are burned in an on-site incinerator. All process waste water goes to the on-site Chemical Waste Water Treatment system which consists of stripping the volatile solvents, neutralization, flocculation, separation of solids and biological treatment. The resulting waste water is discharged to the City of Basle Sewage Treatment plant and finally into the Rhine River. This procedure is in compliance with the permit issued by the Construction Supervision Department of the Canton of Basel-Stadt (= Bauinspektorat des Kantons Basel-Stadt) and the Water Protection Agency (= Kantonales Gewaesserschutzamt).

Solids Controls - All solid process residuals (e.g. dusts, filter residues or rejected production material) are burned on-site in a rotary kiln at approximately 1200°C. The residues of the incineration process are washed with water (which is fed to the industrial waste water pipe system) and then sent off site for disposal. The incinerator plant must operate in conformance with permits issued by the Swiss Association of Owners of Pressure Vessels (= Schweizerischer Verband der Druckbehaelterbesitzer) and the Construction Supervision Department of the Canton of Basel-Stadt (Bauinspektorat des Kantons Basel-Stadt).

b) Schweizerhalle, Canton of Basel-Landschaft, Switzerland

Air Controls - Air emissions stemming from the synthesis of bulk drug substances are controlled by equipment such as surface condensers, brine-cooled vent condensers (-15°C) and scrubber systems operating with either plain water or acidic, basic or oxidizing aqueous solutions. Air emissions from the on-site incinerator are controlled by a series of scrubbers operating with aqueous absorption mediums. The equipment is in compliance with permits of the Department of Commerce, Industry and Employment of the Canton of Basel-Landschaft (= Amt fuer Gewerbe, Handel und Industrie des Kantons Basel-Landschaft) and the Department of Air Pollution Control (= Lufthygieneamt).

Liquid Controls - All waste solvents are burned in an on-site incinerator. All process waste water goes, if necessary after on-site pretreatment, to the "ARA Rhein", a public-owned Joint Waste Water Treatment Plant. The effluent of this plant is discharged into the Rhine River. This procedure is in compliance with the permit issued by the Department of Commerce, Industry and Employment of the Canton of Basel-Landschaft (= Amt fuer Gewerbe, Handel und Industrie des Kantons Basel-Landschaft) and the Water protection Agency (= Kantonales Gewaesserschutzamt).

Solids Controls - All solid process residuals (like dusts, filter residues or rejected production material) are sent to the rotary kiln, working at approximately 1200°C, owned by CIBA-GEIGY at the Basle site (see above).

c) Stein, Canton of Aargau, Switzerland

Air Controls - Air emissions from operations relevant to this product are controlled by equipment such as filter type dust collectors. A house vacuum is used to control dust created by process equipment, clean up minor spills and clean equipment between operations. All emission points are operated to comply with permits issued by the Department of Industry and Commerce of the Canton of Aargau (= Industrie und Gewerbeamt des Kantons Aargau).

Liquid Controls - Waste solvents are sent to the incinerator owned by Ciba-Geigy at the Schweizerhalle site (see above). The waste water is discharged for purification to the Sewage Treatment Plant of the City of Bad Saeckingen (Federal Republic of Germany) and is in compliance with permits issued by the Department of Water protection of the Canton of Aargau (=Abteilung Gewaesser des Kantons Aargau) and the Joint Association for Sewage Water Treatment of the Cities of Stein and Bad Saeckingen (= Abwasserverband Stein-Bad Saeckingen).

Solids Controls - All solid process residuals (e.g. dusts, filter residues or rejected production materials) are sent to the rotary kiln, working at approximately 1200°C, owned by CIBA-GEIGY at the Basle site (see above). All packaging components that can be recycled are sold to Switzerland, for that purpose. Aluminum containing tablet packaging components are separated out and sent to Switzerland, for recycling.

d) Summit, New Jersey

Air Controls - Air emissions from packaging operations relevant to this product are controlled by equipment such as bag house and filter type dust collectors. A house vacuum is used to control dust created by process equipment, clean up minor spills and clean equipment between operations. All emission points will be operated to comply with permits issued by the NJDEP.

Liquid Controls - All process water is discharged for final treatment to the Joint Meeting Sewage Treatment Plant, Elizabeth, New Jersey and will be in conformance with the permit issued by them.

Solids Controls - All solid process residuals (e.g. dusts, rejected production material) are sent off site for incineration at either

facilities. All sites must operate in conformance with permits issued under the authority of the Resource Conservation and Recovery Act (RCRA) and applicable Federal and state regulations. All packaging components that can be recycled are sold to for that purpose.

e) Suffern, New York

Air Controls - Air emissions from packaging operations relevant to this product are controlled by dust collectors. A house vacuum system is used to control dusts created by process equipment, clean up minor spills and clean equipment between operations. All emission points are operated to comply with permits issued.

Liquid Controls - All process waste water is discharged to the Village of Suffern Publicly Owned Treatment Works, in compliance with a permit issued by the Village of Suffern. No waste water is pretreated.

Solids Controls - [redacted] solid process residuals (e.g. dusts, solvents, rejected production material) are sent off site for incineration at a facility operating in conformance with permits issued under the authority of the Resource Conservation and Recovery Act, and applicable Federal, state and local regulations. Packaging components which can be recycled are sold.

2) Citations

a) Basle, Canton of Basel-Stadt, Switzerland
b) Schweizerhalle, Canton of Basel-Landschaft, Switzerland
c) Stein, Canton of Aargau, Switzerland

All the Ciba-Geigy facilities in Switzerland must be in compliance with the following regulations issued by the Swiss Federal Government:

Air Citations - Federal Air Pollution Control Regulation ="Luftreinhalteverordnung" (LRV) 814.318.142.1 (12/16/85, latest edition 1/1/87).

Water Citations - Federal Regulation to Introduce Waste Waters into Rivers and Lakes = "Verordnung ueber Abwassereinleitungen" 814.225.21 (12/8/75, latest edition 4/1/87).

Solids Citations - Federal Regulation for the Transport and Disposal of Special Waste ="Verordnung ueber den Verkehr mit Sonderabfaellen" (11/12/86).

d) Summit, New Jersey

Air Citations - Air emissions must be in compliance with New Jersey air pollution control regulations as found in the New Jersey Administrative Code (NJAC) of Regulations, Title 7, Chapter 27, subchapters 1 through 18. This represents all applicable Federal and state requirements for air emissions under the direction of the New Jersey Department of Environmental Protection (NJDEP). Each source is regulated by a unique Certificate to Operate issued by the NJDEP. No local permits are required for these operations.

Water Citations - Aqueous emissions must be in compliance with the Clean Water Act. New Jersey is an authorized state and regulates these emissions under the authority of NJAC Title 7, Chapter 14A, Subchapters 1 through 13. It is under this authority that the NJDEP regulates the Joint Meeting Sewage Treatment Plant of Elizabeth which operates by control of NJPDES permit #NJ0024741. The Summit facility is regulated in turn by the Joint Meeting as a Significant Industrial User under authority granted it by the NJDEP. The facility must maintain compliance with permit #JM-5510 issued it by the Joint Meeting.

Solids Citations - The NJDEP has obtained authorization from the EPA to administer all aspects of the regulations promulgated under the authority of RCRA. The applicable NJDEP regulations can be found at NJAC Title 7, Chapter 26, Subchapters 1 through 15. All solid wastes must be disposed of in accordance with these regulations. For hazardous solid wastes, the Summit facility operates under interim status permit #ND001316173. Since all solid wastes are sent off site for disposal, this requires the use of EPA/NJDEP-permitted transporters and disposal facilities.

e) Suffern, New York

Air Citations - Each source must be in compliance with a Certificate to Operate issued under the regulations set forth by the New York State Department of Environmental Conservation Environmental Regulatory Program, Title 6, New York Codes, Rules and Regulations. No local permits are required.

Water Citations - Aqueous emissions must be in compliance with the Clean Water Act. The Suffern plant discharges waste water to the Village of Suffern Publicly Owned Treatment Works (POTW), under a permit issued by the Village of Suffern. The POTW, in turn, operates under a State Pollutant Discharge Elimination System (SPDES) permit issued by the State of New York under the above mentioned Title 6 NYCRR.

Solids Citations - The New York Department of Environmental Protection has obtained final authorization from the EPA to administer all aspects of the regulations under the authority of RCRA. The applicable regulations are included in Title 6 NYCRR. All solid wastes must be disposed of in accordance with these regulations. For hazardous solid wastes, the Suffern plant operates under interim status permit #NYD013238480. Since all solid wastes are sent off site for disposal, this requires the use of permitted transporters and disposal facilities.

7. Fate of Emitted Substances in the Environment

A. Physical Chemistry of the New Drug Substance

The physical chemistry of Aredia™ is described in reports contained in Item 3 of this NDA. Copies of the pertinent reports can be found in Appendix III.

B. Summary of Biodegradation and Pharmacokinetics

Pamidronate disodium was tested for ready biodegradability in the modified Sturm test (OECD - Guideline, No. 301 B, 1981). Biodegradation was calculated as 2% in 28 days for 50.3 mg/L.

Urinary excretion of pamidronate disodium accounted for an overall mean 51% (32-80%) of the dose within 72 hr of a 60-mg intravenous dose infused over 4 or 24 hr in cancer patients with minimal or no bony involvement. Body retention during this period was therefore calculated to be a mean 49% (20-68%) of the dose or 29.3 mg (12-41 mg) of pamidronate disodium. The urinary excretion rate profile exhibited biphasic disposition characteristics with an alpha half-life of 1.6 hr and a beta half-life of 27.2 hr.

In one animal study after intravenous administration, approximately 50-60% of the compound was rapidly taken up by adsorption to bone and slowly eliminated from the body by the kidneys. In rats given 10 mg/kg bolus injections of pamidronate disodium, approximately 30% of the compound was found in the liver shortly after administration and was then redistributed to bone or eliminated by the kidneys over 24-48 hr. Studies in rats injected with radioactive pamidronate disodium showed that the compound was rapidly cleared from the circulation and taken up mainly by bones, liver, spleen, teeth, and tracheal cartilage. Radioactivity was eliminated from most soft tissues within 1 to 4 days, was detectable in liver and spleen for 1 and 3 months, respectively, and remained high in bones, trachea, and teeth for up to 6 months after dosing. Bone uptake occurred preferentially in areas of high bone turnover. Both single and repeated administration of 1 mg/kg Aredia™ intravenously in rats resulted in predominant uptake to bones, with highest concentrations in tibia, thoracic vertebrae and cranium.

8. Environmental Effects of Released Substances

A. Bulk Chemical Production

Bulk chemical production of pamidronate disodium does not result in any release of drug substance into the environment. Liquid aqueous waste generated during production is fed to the Chemical Waste Water Treatment Plant, where any active substance is precipitated by the routine addition of calcium hydroxide. Cleaning of process equipment (e.g., vessels, dryers, etc.) may result in the discharge of small quantities of product into the plant process waste water stream which is fed to the W.W.T. plant and treated as decribed above. The effects of pamidronate disodium on aquatic organisms in liquid waste streams have been found to be of minor importance:

Determination of LC50 (96h) with ZEBRA FISH (Brachydanio rerio) according to OECD-Guideline for Testing of Chemicals No. 203 (1984) gives the following result:
LC50 (96h) > 100 mg/L
Values are based on nominal concentrations.

Determination of EC50 (24h) with DAPHNIA MAGNA STRAUS 1820 according to OECD-Guideline No. 202 (1984) gives the following result:
EC50 (24h) > 100 mg/L
Values are based on nominal concentrations.

Determination of IC_{50} in AEROBIC BACTERIA according to OECD-Guideline No. 209 (1984) gives the following result:
IC_{50} = > 100 mg/L

B. Drug Product Production

Production of Aredia™ Vials and Ampuls may result in the generation of small amounts of solid and liquid wastes. Solid waste (e.g., collected dusts and rejected product) will be incinerated. The amount of liquid waste generated during the cleaning of production equipment and discharged into the plant process waste water stream is not expected to be significant.

C. Aredia™ Vials and Ampuls Use

Aredia™ Vials and Ampuls administered to patients will enter the environment primarily in the urine and feces as unchanged drug or as metabolites.

At the recommended daily dose, the total amount of pamidronate disodium and metabolites at any single waste treatment site would not appear to be consequential.

D. Toxicology Summary

Aredia™ exhibited a low to moderate order of acute toxicity in mice, rats and rabbits dosed by oral and parenteral routes. In repeat dose studies, the pharmacologic activity of the compound to decrease bone turnover resulted in bone changes in rats and dogs, including increased length of the primary spongiosa and prominent bone-osteoid seams. Other findings included local irritation at the injection site in all repeat dose parenteral studies, partially reversible nephropathy in several rat and dog studies, and mortality and systemic toxicity in dogs treated at higher doses for one month. Carcinogenicity studies in rats and mice are currently being evaluated.

No evidence of embryotoxicity, fetotoxicity or teratogenicity was noted in a Segment II study in rabbits. F_1 generation offspring derived from rats treated orally with Aredia™ (150 mg/kg) demonstrated reduced fertility when mated with each other but not when mated with untreated rats.

Aredia™ was not mutagenic in the Ames Assay (with and without metabolic activation), the Nucleus Anomaly Test, Sister Chromatid Exchange Study and the Point Mutagen Test.

E. Conclusion

Based on these data, no adverse short or long-term effects are anticipated as a consequence of the release of Aredia™ into the environment at levels associated with its production or use.

9. Use of Resources and Energy

The raw materials utilized to manufacture Aredia™ Vials and Ampuls are common compounds all of which are in ample commercial supply. Energy commitment for bulk chemical and dosage form production in the United States is nominal and not excessive. Only very small increases in the utilization of energy are anticipated since production occurs at existing facilities. The expected product volume will not significantly increase the consumption of those resources beyond levels presently experienced.

No effects upon endangered or threatened species and upon property listed in or eligible for listing in the National Register of Historic Places are anticipated.

10. Mitigation Measures

No potential adverse environmental impacts are forseen with the production and use of Aredia™ Vials and Ampuls.

The manufacture, distribution and use of the drug product takes place under highly regulated and controlled conditions which further mitigate against negative environmental consequences. Processors named in this application are in compliance with local and Federal Regulations.

11. Alternatives to the Proposed Action

The only alternative to the action is withholding approval of the Application, resulting in denying the drug to the United States market. As the use of Aredia™ Vials and Ampuls will directly benefit patients requiring therapy for hypercalcemia associated with malignancy, withholding approval is not recommended.

Approval of the Aredia™ Vials and Ampuls New Drug Application is justified from an environmental perspective and is preferable to non-approval.

12. List of Preparers

This assessment was prepared by:

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 preparation of the environmental assessment.

For Linda R. Cassidy
J. Cohen, Director
Technical Services & Administration