CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020740

CHEMISTRY REVIEW(S)

JUN - 3 1997

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 20-740 **CHEMISTRY REVIEW #: 2** **DATE REVIEWED:** 03-JUN-1997

Submission Type	Document Date	CDER Date	
Original	26-JUN-1996	26-JUN-1996	**User fee I.D. Nº 3031**
Amendment	28-MAY-1997	29-MAY-1997	

NAME & ADDRESS OF APPLICANT: Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175
Phone (203) 937-2000 931-5145

DRUG PRODUCT NAME

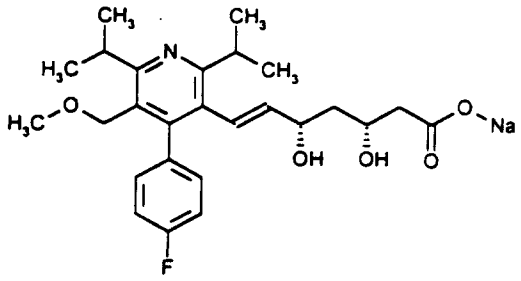
Proprietary:	BAYCOL
Nonproprietary/Established/USAN:	Cerivastatin Tablets
Code Name	BAY w 6228
Chem. Type/Ther. Class:	**1 S**

PHARMACOLOGICAL CATEGORY/INDICATION: HMG-CoA reductase Inhibitor. Hypercholesterolemia.

DOSAGE FORM: Tablets **STRENGTHS:** 50, 100, 200 and 300 µg

ROUTE OF ADMINISTRATION: Oral
DISPENSED: R

CHEMICAL NAME/ STRUCTURAL FORMULA:



$C_{26}H_{33}FNO_5Na$

F.W. = 481.5 g/mol

Bay w 6228 (Bayer Code Nº)

CAS Nº 143201-11-0

(+)-3*R*,5*S*-Sodium (*E*)-7-[4-(4-florophenyl)-2,6-diisopropyl-5-methoxymethyl-pyrid-3-yl]-3,5-dihydroxy-6-heptenoate

CONCLUSIONS & RECOMMENDATIONS: The applicant has provided adequate and satisfactory response to the minor deficiencies stated in the Agency correspondence to the manufacturer. The application can be **approved** from the Chemistry viewpoint. EER acceptable as of 17-APR-1997.

Orig. NDA 20-740
cc: HFD-510/Division File
HFD-510/RMisbin/SMoore/JRhee/MSimoneau/XYsern
HFD-820/Gibbs

Xavier Ysern, PhD

R/D Init by:

filename: 20740_2.nda

6/3/97

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020740

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-740

Baycol (cerivastatin)

Tablets 50, 100, 200, 300 μg

Division of Metabolic and Endocrine Drug Products

(HFD-510)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-740

Baycol (cerivastatin)

Tablets 50, 100, 200, 300 μg

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 this action 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 Baycol, Bayer Corporation, Pharmaceutical Division has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Cerivastatin is a chemically synthesized drug which is administered as tablets (50, 100, 200, and 300 µg). Cerivastatin is administrated orally in the treatment of hypercholesteremia. The proprietary intermediates for the drug substance are manufactured by Bayer AG, Wuppertal, Germany. The drug substance, drug product manufacturing and packaging occurs at the Bayer AG facility in Köln (Cologne), Germany. Packaging will also occur at Bayer, West Haven, CT. The finished drug product will be used in throughout the United States.

Cerivastatin may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. Therefore, the applicant has submitted a tier 0 EA without format items 7, 8, 9, 10 and 11 in accordance with the *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, Center for Drug Evaluation and Research (CDER), November 1995.*

Disposal of the 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. In the US, returned

drug product and packaging waste will be disposed of by incineration via a manifested isolated disposal program. 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.

5/2/97
DATE

Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

5/2/97
DATE

Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

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

Environmental Assessment

3.3

ENVIRONMENTAL ASSESSMENT INFORMATION

Cerivastatin Drug Product

1. Date: May 20, 1996

2. Name of Applicant/Petitioner: Bayer Corporation
Pharmaceutical Division

3. Address: 400 Morgan Lane
West Haven, CT 06516

4. Description of the Proposed Action:

The proposed action is manufacturing and packaging of Cerivastatin Tablets (0.05 mg, 0.1 mg, 0.2 mg and 0.3 mg) for the purpose of sale to the general public. Cerivastatin will be administered orally in the treatment of hypercholesteremea. This product will be used by consumers throughout the United States.

a. Production of Intermediates:

The intermediates in the synthesis of Cerivastatin are not available in the open marketplace and will be produced at Bayer AG's Wuppertal-Elberfeld facilities in

Friedrich Ebert Strasse 217-399
D-42096 Wuppertal, Germany

The facilities are located in an urban environment. The surrounding area is hilly with a temperate climate.

b. Drug Substance and Drug Product Manufacturing and Packaging:

The Cerivastatin drug substance (Bay W6228) is produced at the Bayer AG's production facility in

Berliner Strasse 156
D-51063 Köln (Cologne), Germany

In the first step of the drug manufacturing process any unacceptable material will be returned to Bayer AG's Wuppertal-Elberfeld facilities.

The drug product will be manufactured and packaged in the existing Cologne pharmaceutical manufacturing facilities. Cologne is an urban setting with generally flat terrain and has temperate climate.

During the manufacturing of the product in Cologne, all Cerivastatin goods and packaging waste products will be collected for disposal at the Leverkusen site. Actual disposal will be managed through the office of environmental and safety affairs located in Leverkusen. All returned goods and manufacturing wastes are disposed of by incineration via a manifested isolated disposal program. The current main incineration facility for Bayer AG, Pharmaceutical Division is located in Leverkusen. This is a permitted hazardous waste treatment, transfer and recovery facility for which Bayer AG holds all necessary licenses. The facility is regularly inspected by the Hazardous Waste personnel from the State of North Rhine-Westphalia.

The majority of the manufacturing waste sent to the Leverkusen incinerator is typically in the form of bulk tablets and / or bulk intermediate.

Cerivastatin tablets will also be packaged in the existing pharmaceutical manufacturing facilities at Bayer Corporation's Pharmaceutical Division's West Haven, CT location. West Haven is in a urban setting with a generally flat to slightly hilly terrain and has a temperate climate.

Cerivastatin tablets will be packaged in unit dose aluminum blisters and square white opaque plastic bottles with safety seals and child-resistant closures.

During the packaging of the product in West Haven, all Cerivastatin goods and packaging waste products will be collected for disposal at the West Haven site. Actual disposal will be managed through the office of the manager of environmental and safety affairs located in West Haven. All returned goods and packaging wastes are disposed of by incineration via a manifested isolated disposal program. The current main incineration facility for Bayer Corporation is is located at This is a permitted hazardous waste treatment, transfer and recovery facility with Environmental Protection Agency (EPA) identification number MAD053452637. As a permitted TSDF, the facility is regularly inspected by the Hazardous Waste personnel from both the State of Massachusetts as well as the Federal EPA. is located in an industrial urban setting on the water front in the greater Boston area.

The incineration process utilized for the destruction of product waste from the West Haven site is a It's main chamber is of a design with a that is capable of processing approximately of material at a temperature of approximately The second stage is a fixed hearth chamber where at temperatures in excess of Following the is a designed and managed for

Materials sent to the incinerator in finished product form are either in The majority of the finished product waste will either be in the form of bulk tablets and/or packaging in

5. Description of drug and identification of the chemical substance that is the subject of this proposed action:

Cerivastatin will be administered orally in the treatment of hypercholesteremea.

The intermediates in the synthesis of Cerivastatin are manufactured at the Bayer AG's Wuppertal-Elberfeld Facility in Germany and will be transported to the Cologne Facility in Germany for use in drug substance synthesis, drug product manufacturing and packaging. Cerivastatin tablets will also be transported to the Bayer Corporation's Pharmaceutical Division's, West Haven, Connecticut site for packaging.

Drug Name:	Cerivastatin
Molecular Weight:	481.5 g/mole
CAS Number:	143201-11-0
Molecular Formula:	Empirical $C_{26}H_{33}FNO_5Na$
Name:	(+)-[3R,5S,(E)]-sodium-7-[4-(4-fluorphenyl)-2,6-diisopropyl -5-methoxymethylpyrid-3-yl]3,5-dihydroxyhept-6-enoate
Description:	White to almost white amorphous powder

A material safety data sheet for Cerivastatin (Bay W 6228) can be found in Appendix 1.

There are no impurities present at levels exceeding 1%.

6. Introduction of substances into the environment:

6a. Intermediates manufactured at the Bayer AG's Wuppertal-Elberfeld facilities:

may be emitted during the manufacture of intermediates. Liquid wastes from process and cleaning operations containing are collected and transferred to the waste water treatment plant (WWTP) on site, where insoluble material is separated by sedimentation and remaining contaminants are removed by biological degradation. Special liquid wastes which are

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not allowed to enter the WWTP and discharges from analytical operations are collected and disposed of in incineration facilities approved for disposal of industrial wastes.

Emissions are controlled routinely by the staff of Bayer AG's Department of Environmental Protection (WV-Umweltschutz) to assure compliance with the Federal Emissions Control Act (BImSchG) of the Federal Republic of Germany. According to this act, each manufacturing installation, regardless of the type of operation, is designated as a single "point source" which may not exceed the established emission limits. Waste water residues from the point source must be channeled to a specific WWTP. Water from the treatment plant must meet the requirements for "Treated Water" as established in the "Decree on the Disposal of Waste Water". According to the Technical Regulations on Waste Control, all solid organic residues resulting from the operation must be incinerated in a facility approved for disposal of industrial waste. Ash from the incinerator must be disposed of in a licensed landfill. A list of environmental laws and regulations which regulate Bayer AG are included in Appendix 2.

According to BImSchG the production of pharmaceutical active ingredients is further subject to the "Prevention of Harmful Effects on All Compartments of the Environment", e.g. Air Pollution, Water Pollution, Land Pollution, Noise, Vibration and Similar Phenomena.

Bayer AG holds all required licenses to manufacture pharmaceutical active ingredients and intermediates, as well as Cerivastatin and the Cerivastatin-precursor Bay 8877 in its Wuppertal-Elberfeld facilities. The licenses are granted by the Administrative District of Dusseldorf as outlined by the Federal Emissions Control Act. Records of emission controls carried out are maintained by Bayer AG's Department of Environmental Protection. Production of Cerivastatin intermediates in the Wuppertal-Elberfeld facilities is carried out in full compliance with the Federal Emissions Control Act. The anticipated increase in production volume will not cause emissions in excess of the present licensed limits. A Certificate of Compliance for Bayer AG's Wuppertal-Elberfeld facilities is included in Appendix 3.

6b. Drug substance and drug product manufacturing and packaging at Bayer AG's Cologne, Germany:

Cerivastatin tablets, the subject of the NDA, will be manufactured and packaged at the Bayer AG's site in Cologne. The manufacturing of Cerivastatin involves drug substance production and tablet manufacturing operations that include:

- All manufacturing and packaging operations are performed in compliance with Current Good Manufacturing Practices.

Wastes from the manufacturing and packaging of Cerivastatin tablets will be mainly generated in a

Wastes will be managed in such a fashion as to have no significant impact upon the production facilities compliance permit status relative to all federal, state and local environmental and safety laws and regulations in Germany (a list of all applicable environmental and occupational laws/regulations is attached as Appendix 2).

No significant quantities of chemical substances should be emitted to the environment because of the controls exercised during manufacturing and packaging and the use of environmental dust collecting systems. Any product accidentally spilled will be vacuumed up and placed in a sealed container for disposal. The only possible emissions from the cleaning of the manufacturing equipment that will be utilized for this product application, will be the small amounts of dust that may be present on the manufacturing equipment during equipment cleaning. These particles will be washed to a waste water hold up system for further treatment. The waste water is then discharged to the Town of Cologne's POTW in Cologne-Stammheim in compliance with the local waste water discharge permit.

In conclusion, the manufacture and packaging of Cerivastatin at Cologne should have no effect on compliance with existing applicable emission requirements (including occupational) at the federal, state or local level. No modifications of any existing permits will be necessary to manufacture and package this product. A Certificate of Compliance for Bayer AG's Cologne facilities is included in Appendix 3.

6c. Drug product packaging at Bayer Corporation in West Haven, CT:

Cerivastatin tablets, the subject of the NDA, will be packaged at Bayer Corporation's Pharmaceutical Division's site in West Haven, CT. All packaging operations are performed in compliance with Current Good Manufacturing Practices.

Wastes from the packaging of Cerivastatin tablets will be generated
Wastes will be managed in such a fashion as to have no significant impact upon the production facilities compliance permit status relative to all federal, state and local environmental and safety laws and regulations. Information regarding permits for air, liquid and solid emissions is provided. This information includes permit numbers, issuing agencies and the permit expiration dates, if applicable. A list of all applicable federal, state and local environmental and occupation laws/regulations is provided for Bayer Corporation's West Haven location. (see Appendix 4). A Certificate of Compliance for Bayer West Haven, CT is included in Appendix 3.

No significant quantities of chemical substances should be emitted to the environment because of the controls exercised during packaging and the use of environmental dust collecting systems. Any product accidentally spilled will be vacuumed up and placed in a sealed container for disposal. It is felt that the collection efficiency of the dust collection system is quite good and no emissions are anticipated. Once vacuumed,

equipment is then water washed with the waste water being discharged to the Town of West Haven's POTW in compliance with State of CT - DEP discharge # SP0000141, expiration date of 7/31/95 (a new waste water discharge permit application was filed on February 27, 1995).

Dust collection systems in West Haven predominantly utilize pleated filter media of 95% efficiency. Some of the collection systems have media that is simply vibrated to remove contaminant that is then captured into a collection container. Other systems have disposable filter media that is completely removed and disposed of. In either case, materials to be disposed go to the facility previously described, where they are incinerated.

As with all of West Haven's current product manufacturing and packaging wastes, Cerivastatin wastes will be containerized for isolated manifested off-site incineration. The incineration of Cerivastatin wastes should be complete resulting in little or no Cerivastatin being contained in incinerator ash.

In conclusion, the packaging of Cerivastatin at West Haven should have no effect on compliance with existing applicable emission requirements (including occupational) at the federal, state or local level. No modifications of any existing permits will be necessary to manufacture and package this product.

6d. Expected introduction concentration of Cerivastatin:

The Cerivastatin drug substance (Bay W6228) will be put on the US market in the fifth year after receiving marketing authorization in an amount of approximately

The expected introduction concentration (EIC) entering into the aquatic environment from patient use is:

EIC-Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liters per day entering POTW's*
C = year/365 days
D = 10^6 mg/kg (conversion factor)
liters/day entering publicly owned treatment works

EIC-Aquatic (ppm) =

According to CDER's Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements issued November 1995, this E.A. qualifies for a Tier 0-classification. Therefore the format items 7,8,9,10,11 and 15 will not be submitted.

12. List of preparers:

This assessment was prepared by Gary G. Toczylowski, Manager of Environmental and Safety Affairs at Bayer Corporation, Pharmaceutical Division. He is familiar with the operations to be carried out and knowledgeable of the wastes to be generated.

Dr. Bernd Richter, Manager of Environmental and Safety Affairs at Bayer AG, Pharmaceutical Division in Wuppertal-Elberfeld, Germany provided the information on the intermediates, drug substance and drug product manufacturing and packaging at AG's Wuppertal-Elberfeld and Cologne facilities. He is familiar with the operations to be carried out and knowledgeable of the wastes to be generated.

13. Certification:

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

Gary G. Toczylowski
Manager of Environmental and Safety Affairs
Bayer Corporation
Pharmaceutical Division
West Haven, CT

14. APPENDICES

APPENDIX 1 -	Material Safety Data Sheet
APPENDIX 2 -	Bayer AG Environmental Laws and Regulations
APPENDIX 3 -	Certificates of Compliance - Bayer Corporation's Facility in West Haven, CT and Bayer AG's Facilities in Cologne and Wuppertal-Elberfeld, Germany
APPENDIX 4 -	West Haven Regulatory Overview

Appendix 1

Material Safety Data Sheet

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Health Care Sector

MILES

DIN Safety Data Sheet

052802/02

Date of issue: May 5, 1992

U.S.A. Emergency Contact: MILES via CHEMTREC 1-800-424-9300
Washington, DC / Outside U.S.A. 202-483-7616

Commercial product name Bay H 6228

1.1 Chemical characterisation: active drug substance
(+)-3R,5S-Sodium-erythro-(E)-7-[4-(4-fluorphenyl)-2,6-diisopropyl-5-methoxymethyl-pyrid-3-yl]-3,5-dihydroxy-hept-6-enoate
Material type: Phenylpyridyl-Verbindung
1.2 Form: powder (Lyophilisate)
1.3 Colour: white
1.4 Odour: odourless

2. Physical and safety data tested in accordance with
2.1 Change in physical state:
2.2 Density:
2.3 Vapour pressure:
2.4 Viscosity: not applicable
2.5 Solubility in water: highly soluble
2.6 pH value:
2.7 Flash point: not applicable
2.8 Ignition temperature:
2.9 Explosive limits:
2.10 Thermal decomposition: No decomposition when used as directed.
2.11 Hazardous decomposition products:
2.12 Hazardous reactions: No hazardous reaction when used as directed.
2.13 Further information: light-sensitive

3. Transport
GGVSee/IMDG Code: 6.1 UN No.: 2811 MFAG: 4.2 EmS: 6.1 04
GGVE/GGVS: Class 6.1 No. 90C RID/ADR: Class 6.1 No. 90C
ADNR: Class NO No. -- Cat -- ICAO/IATA-DGR: 6.1 2811 III
Postal dispatch approved: no
Declaration for land shipment: PHENYLPYRIDYL-VERBINDUNG ARZNEIWIRKSTOFF
Declaration for sea shipment: Poisonous solids, n.o.s. PHENYLPYRIDYL-COMPOUND (MEDICINE ACTIVE COMPOUND)
Other information:
Harmful. Avoid heat above +30 °C. Keep dry. Irritating to skin and mucous membranes. Keep separated from foodstuffs.

4. Regulations
Labelling of new substances according to § 13 section of the German Chemicals Law/EEC directive 79/831/EEC:
Symbol: T, hazard description: toxic
---- Caution! Substance not yet fully tested.
R 25: Toxic if swallowed.
R 41: Risk of serious damage to eyes.
S 44: If you feel unwell, seek medical advice (show the label where possible).
S 26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

DIN Safety Data Sheet 052802/02

Date of issue: May 5, 1992 Page 02 of 03

Commercial product name Bay H 6228

5. Protective measures, storage and handling

5.1 Technical protective measures:
During handling local official regulations must be observed in order to avert impairment of water by the product.
For storage suitable stores with adequate product-reception volume must be used
Protect from moisture.
Transport temperature not more than +30 °C.
Storage temperature not exceeding +20 °C.
Keep away from light.
Only open product container with local exhaust ventilation.
Only handle product with local exhaust ventilation.

5.2 Personal protective equipment:
Unless the product is entirely enclosed, do not handle it until you have studied the respiratory precautions issued by the appropriate authority or accident prevention association.
Recommended respiratory protection: full mask with filter P3
Eye protection: goggles
Hand protection: gloves of rubber
Other protective equipment: Wear protective clothing.

5.3 Industrial hygiene:
Wash hands before breaks and at end of work.
To clean the floor and all objects contaminated by this material, use plenty of water.
Final cleaning should be carried out with water.
After contact with skin, wash immediately with plenty of water and soap.

5.4 Protection against fire and explosion:
Keep away from naked flame.
Do not empty inner sack above vessels containing a mixture of inflammable gases.

5.5 Disposal:
Product and material polluted with product must be disposed off according to regulations.
Transport in closed, burnable container to suitable incinerator.

6. Measures in case of accidents and fires

6.1 After spillage/leakage/gas leakage:
If product is released it may not be allowed to enter into sewage systems, biological sewage treatment plants, surface waters and/or groundwater.
Avoid formation of dust.
Take up mechanically, fill into labelled, closable containers.
To clean the floor and all objects contaminated by this material, use plenty of water.
Do not let enter into the soil.
Do not rinse into rainwater discharge canal.
Final cleaning should be carried out with water.

6.2 Extinguishing media: All extinguishing materials are suitable.

(to be continued)

DIN Safety Data Sheet

052802/02

Date of issue: May 5, 1992

Commercial product name Bay W 6228

6. Measures in case of accidents and fires (Continuation)

6.3 First aid:
Contamination of the eyes must be treated by thorough irrigation with water, with the eyelids held open. A doctor (or eye specialist) should be consulted immediately.
If you feel unwell, seek medical advice (show the label where possible).
In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

6.4 Further information:
In case of fire care must be taken to collect the quenching water.
Return contained product to the manufacturer.
Combustibility: BZ 3 = local burning or glowing with, at the most, only slight spreading.
Keep away from naked flame.
Cool undamaged containers with water.

7. Information on toxicity

Acute toxicity:
LD_{50} oral, rat: 70 mg/kg

Chemical-pharmacological effect: lipid lowering agent

Micronucleus test: negative (mouse)

Risk of serious damage to eyes.

8. Information on ecological effects

Correct handling will produce no environmental problems.

Water pollution class (WGK): 2 - impairment of water quality
(own classification)
WGK = Classification in accordance with the German Water Resources Act

9. Further information

All tests to the above mentioned data are based on methods generally used in the FRG.
The instructions given here are valid only for the product as supplied, not for derivatives resulting from its use.

BAYER-Storage class: 8

The data given here is based on current knowledge and experience. The purpose of this Safety Data Sheet is to describe the products in terms of their safety requirements. The data does not signify any warranty with regard to the products' properties.

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Appendix 2

Bayer AG Environmental Laws and Regulations

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ENVIRONMENTAL ASSESSMENT

Bayer AG is regulated by the following environmental laws and regulations:

1. **"Bendesemissionsschutzgesetz"** (Federal Law for the Protection of the Environment against the Adverse Influences caused by Contamination of the Air by noise, vibration and similar events). Published in Federal Law Gazette, March 15, 1974, amended August 12, 1980.

2. **"Wasserhaushaltsgesetz"** (Federal Law for the Protection of Water) Published in Federal Law Gazette, October 16, 1976, amended March 28, 1980.

3. **"Abfallgesetz"** (Federal Law for Minimization and Disposal of Waste) Published August 27, 1986.

4. **"TA Luft"** (Clean Air Laws) Published in Joint Ministerial Gazette, February 27, 1986.

5. **"TA Lärm"** (Noise Protections Laws) Published in July 16, 1986.

6. **"Chemikaliegesetz"** (Federal Law for Protection Against Dangerous Chemicals), Published in Federal Law Gazette, September 16, 1980.

7. **"Gefahrstoffverordnung"** (Regulations for Dangerous Products)Published in Federal Law Gazette, August 28, 1986.

8. **"Druckbehälterverordnung"** (Regulations for Pressure Vessels for Compressed Gases) Published in Federal Law Gazette, February 27, 1980.

9. **"Störfallverordnung"** (Federal Law for Protection of the Environment) Published in Federal Law Gazette, June 27, 1980.

10. **"Verordnung über Anlagen Zur Lagerung, Abfüllung und Beförderung brennbarer Flüssigkeiten Zu Lande"** (Regulations for Facilities for Storage, Filling and Transport of Inflammable Liquids on Land) Published in Federal Law Gazette, February 27, 1980, amended May 3, 1982.

11. **"Gefahrgutverordnung Stra_e"** (Regulations for the Transport of Dangerous Products by Road) Published in Federal Law Gazette, July 22, 1985.

12. **"Gefahrgutverordnung Eisenbahn"** (Regulations for the Transport of Dangerous Products by Railway) Published in Federal Law Gazette, July 22, 1985.

ENVIRONMENTAL ASSESSMENT

13. **"Gefahrgutverordnung See"** (Regulations for the Transport of Dangerous Products by Sea) Published in Federal Law Gazette, July 27, 1985.

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14. **"Gefahrgutverordnung Binnenschiffahrt"** (Regulations for the Transport of Dangerous Products on Waterways within Germany) Published in Federal Law Gazette,March 24, 1983.

15. **"IATA - DGR"** (Dangerous Goods Regulations, 28th edition.

16. **"Verordnung über Trinkwasser und über Wasser für Lebensmittelbetriebe"** (Regulations for Drinking Water and Food Handling Factories) Published Federal Law Gazette, may 22, 1986

17. **"Futtermittelgesetz"** (Federal Law on Feedstuffs) Published in Federal Law Gazette July 2, 1975.

18. **"Futtermittelverordnung"** (Regulations on Feedstuffs) Published in Federal Law Gazette, April 8, 1981.

19. **"Arbeitstättenverordnung"** (Regulations for the Working Place) Published Federal Law Gazette, May 20 , 1975

ENVIRONMENTAL ASSESSMENT

Appendix 3

Certificates of Compliance for
Bayer Corporation's Facility in West Haven, CT
and
Bayer AG's Facilities in Cologne and Wuppertal-Elberfeld, Germany

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ENVIRONMENTAL ASSESSMENT

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

May 21, 1996

Environmental and Safety Compliance Statement

Bayer Corporation states it is in compliance with all environmental and safety emission requirements set forth in permits applicable to the packaging of Cerivastatin tablets at its facilities in West Haven, CT, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the packaging of Cerivastatin tablets at its facilities in West Haven, CT. There are currently no pending environmental or safety consent decrees and/or administrative orders against this facility concerning any emission standard.

Gary G. Toczylowski
Manager, Environmental and
Safety Affairs

ENVIRONMENTAL ASSESSMENT

CERTIFICATE

To whom this may concern

It is hereby certified that the company

Bayer AG

with company headquarters in Leverkusen, Germany has permits to manufacture pharmaceuticals at its plant situated at

Berliner Str. 156
D-51063 Köln (Cologne), Germany

under the relevant German laws for the protection of the environment.

Bayer AG is in compliance with all environmental and safety emission requirements set forth in permits applicable to the production of Cerivastatin at its facilities in Köln, Germany as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the production of pharmaceuticals.

There are currently no pending environmental or safety consent decrees and/or administrative orders against this facility concerning any emission standard.

H.Stillings
Bayer AG
PH-TO LEV 1

CERTIFICATE

To whom this may concern

It is hereby certified that the company

Bayer AG

with company headquarters in Leverkusen, Germany has permits to manufacture pharmaceutical active ingredients at a plant situated at

Friedrich Ebert Str. 217 - 319
Wuppertal- Elberfeld
Germany

under the relevant German laws for the protection of the environment.

Bayer AG is in compliance with all environmental and safety emission requirements set forth in permits applicable to the production of Cerivastatin drug product Bay W 6228 and its precursor Bay W 8877 at its facilities in Wuppertal, Germany as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the production of pharmaceutical active ingredients.

There are currently no pending environmental or safety consent decrees and/or administrative orders against this facility concerning any emission standard.

Dr.H.Diehl
BAYER AG
PH-TO Elberfeld

Appendix 4

West Haven Regulatory Overview

APPEARS THIS WAY

WEST HAVEN REGULATORY OVERVIEW

The proposed application to package Cerivastatin Tablets in the exiting Corporation facility located in West Haven, Connecticut could impact the following federal, state and local environmental and safety laws and regulations that the site is currently in compliance with. However, there are no negative impacts anticipated due to the small size of the proposed activity, as well as internal handling procedures that have been designed to mitigate these potential impacts.

1) State of Connecticut DEP, Regulations for the Abatement of Water Pollution. (Current permit # SP0000141, expires 7/31/95, permit renewal application submitted in first quarter of 1995).

2) State of Connecticut DEP, General Permit for the Discharge of Stormwater Associated with Industrial Activity. (No Permit # required only notification. Notification made on 11/20/92).

3) Federal EPA and State DEP, Hazardous and Solid Waste Regulations. (EPA # CTD046418059).

4) Federal EPA and State DEP, biomedical Waste Disposal and Tracking. (No Permit Required).

5) State DEP, Oil and Chemical Release Reporting Requirements. (No Permit Required).

6) OSHA, Response to Hazardous Waste and Handling of Hazardous Materials Release Emergencies, (HAZWOPER). (No Permit Required).

7) State of Connecticut DEP, Regulations for the Abatement of Air Pollution. (Three permits exist on site. All are associated with our fuel burning equipment on site, i.e., 2 boiler installations and 1 emergency generator). None of the dust collection or equipment utilized in the manufacture of products in West Haven has or requires DEP permits, due to the small size and lack of hazardous materials processed in them.

8) Federal Occupational Safety and Health Administration (OSHA) programs also apply to the West Haven facility. Although permits are not required, compliance with a wide variety of occupational safety programs is. In particular, OSHA regulatory required programs that impact the West Haven location the most include: the laboratory standard, blood borne pathogens, respiratory protection, lockout/tagout, personal protective equipment, hazard communication and process safety management.

ENVIRONMENTAL ASSESSMENT

Introduction

Summary

Cerivastatin (Bay w 6228) is a synthetic, pure enantiomeric, which is a very hygroscopic, amorphous powder and therefore very difficult to handle in a manufacturing setting.

For this reason the drug substance is not isolated and the synthetic precursor Bay w 8877 is used as the starting material for the production of the tablets.

Background

All attempts to obtain Bay w 6228 in a form were not successful and the solid could only be obtained by The resulting was difficult to handle and for large scale production the cost to engineer a facility to handle this product would have been prohibitive. For this reason a process was needed to avoid the
The initial process involved f Bay w 8877 followed by a step to isolate the Bay w 6228 followed by the drug to be used as the for manufacturing the tablets. From this process it was evident that the step could be eliminated and the solution from the could be used directly as the for the manufacture of the tablets.
The manufacturing processes described in this NDA support the isolation of the synthetic precursor Bay w 8877 (which has been fully characterized), the to Bay w 6228 and use of the resulting solution for the manufacturing process for the drug product. The purity of the drug substance is controlled by assuring the quality of Bay w 8877 and the Bay w 6228 is tested to assure the quality of the drug substance.