

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020766

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT**

**FOR
XENICAL™**

(orlistat)

Capsules 60 mg and 120 mg

NDA 20-766

Division of Metabolic and Endocrine Drug Products

(HFD-510)

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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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 XENICAL™, Hoffmann-La Roche, Inc. has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Orlistat is a chemically synthesized drug which is administered as 60 mg and 120 mg capsules as a long-term antiobesity medication throughout the United States. Drug substance production operations occur at five different foreign facilities identified in the EA. The drug substance is shipped to the firm's facility in Nutley, New Jersey where the drug product is manufactured.

Chemical and physical test results indicate that orlistat will most likely be restricted to the terrestrial/aquatic environment and will be immobilized on soil/sludge particles and therefore only marginally available to environmental organisms.

As orlistat is expected to persist in the environment for some time, the toxicity of orlistat to terrestrial/aquatic organisms was characterized. Results of the ecological tests showed the most sensitive environmental organisms were *Daphnia* (water fleas) and green algae in which the no effect concentration was greater than the expected environmental concentration by a factor of ca.

█ The data suggest that no significant effects are likely to be observed in the

terrestrial/aquatic environment.

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. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incinerator. 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.

01/13/97
DATE

/S/ [REDACTED]

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

1/15/97
DATE

/S/ [REDACTED]

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)

APPEARS THIS WAY ON ORIGINAL

ORIGINAL NEW DRUG APPLICATION

ENVIRONMENTAL ASSESSMENT

XENICAL® (ORLISTAT, Ro 18-0647)

CAPSULES

1. DATE

September 3, 1996

2. NAME OF APPLICANT

Hoffmann-La Roche Inc.

3. ADDRESS

340 Kingsland Street
Nutley, New Jersey 07110

4. DESCRIPTION OF PROPOSED ACTION

a. Requested Approval

Hoffmann-La Roche Inc. is filing a New Drug Application pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Xenical (Orlistat) capsules (60 and 120 mg strength). It will be packaged in HDPE bottles fitted with and without a child-resistant closure with taseal and silica gel. This Environmental Assessment (EA) has been submitted pursuant to 21 CFR 25.31 a(a).

b. Need for Action

Xenical will be used in humans as an antiobesity medication for use throughout the United States. The drug will be used for the long-term treatment of obesity.

c. Production Locations

The manufacturing of Xenical (Orlistat) will be carried out in six locations:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

The manufacturing responsibilities are as follows:

- The [REDACTED] of the intermediate Ro 19-3052 (step 1- 4) will be carried out by [REDACTED] or at the facilities of [REDACTED]
- The manufacturing of Orlistat (step 5) will be carried out at the facilities of [REDACTED]
- [REDACTED] of Orlistat will be carried out at the facilities of [REDACTED]
- The final dosage form, Xenical capsules will be produced at the Hoffmann-La Roche Inc. site in Nutley, New Jersey. The capsules will be packaged at the Hoffmann-La Roche Inc. facility in Nutley, New Jersey.

The detailed description of the six manufacturing sites are as follows:

[REDACTED]

[REDACTED] The company employs approximately [REDACTED] workers. The plant is erected on an area of approximately [REDACTED] in the neighborhood of other chemical companies and the [REDACTED] steel manufacturer [REDACTED]. It was founded in 1939. At present, it is a part of the [REDACTED] multinational, DSM holding. The manufacturing is primarily of [REDACTED]. Besides production, the company also maintains a small research unit.

[REDACTED] The street address for the [REDACTED]

[REDACTED] The company employs [REDACTED] workers. It is a research and development as well as production site for [REDACTED]. It was founded in [REDACTED] and covers approximately [REDACTED] area. Primarily, it manufactures pharmaceuticals as well as pharmaceutical intermediates. More than [REDACTED] % of the production is exported to more than 50 countries in the world.

F. Hoffmann-La Roche Ltd., Basle, Switzerland: The Roche Basle plant is located on Basle city ground in a mixed industrial and residential zone at the Rhine river. The Basle plant occupies approximately [REDACTED] area and is mostly covered with buildings. In the close proximity, the Ciba-Geigy and Sandoz plants are located northwest of the Roche plant. The Roche Basle plant is a manufacturing site for pharmaceuticals and chemicals for the Roche group. It is also a research and administrative site (Corporate headquarters) for the Roche group.

Roche AG, Sisseln, Switzerland: Roche AG Sisseln is located on the grounds of the two communities Sisseln and Eiken in Switzerland, approximately 12 to 13 miles east of Basle in an industrial zone adjacent to the Rhine river. The facility is run by the Roche Vitamins division which employs approximately [REDACTED] employees. The Sisseln plant occupies approximately [REDACTED] area which was founded in 1958. The Sisseln plant is primarily a manufacturing site for vitamins and pharmaceutical active substances. In addition chemical-technical work is also performed at the site. To be in compliance with various environmental protection regulations, the plant operates a facility for waste air incineration from production units as well as a six stage waste water treatment plant.

[REDACTED] is located in the southern part of [REDACTED] near the airports of [REDACTED] Italy. The site covers an area of approximately [REDACTED] along the main highway connecting northern and southern Europe. The company employs twenty workers. In the last two decades, it has been manufacturing and developing fluid jet mill systems and focusing on contract micronization for pharmaceutical companies all over the world.

Hoffmann-La Roche Inc., Nutley, New Jersey: The street address for the Hoffmann-La Roche Inc. plant is 340 Kingsland Street, Nutley, New Jersey 07110. The Hoffmann-La Roche Inc. plant is located

approximately 10 miles west of New York City in Nutley, New Jersey. The Nutley plant is located in an industrial/residential area. The state highway 3 runs along the north boundary of the site. The Passaic river is located approximately one mile east of the plant. The Nutley plant occupies approximately [REDACTED] of land and mostly occupied by office, research and manufacturing buildings. The entire state of New Jersey is a non-attainment zone for ozone. The Nutley environs are in attainment for all other criteria pollutants. The Roche Nutley plant is a manufacturing site for pharmaceuticals and chemicals for the Roche group. It is also a research and an administrative site (US headquarters) for the Roche group.

d. Locations of Use

Xenical drug product primarily will be used in patients' homes and to some extent in hospitals and clinics throughout the United States.

e. Disposal Sites

Returned, expired or rejected drug product will be returned to Hoffmann-La Roche Inc. in Nutley, New Jersey for disposal. The returned, expired or rejected product will be incinerated in an on-site medical waste incinerator or will be shipped to an off-site licensed commercial incinerator. The permit number for on-site medical waste incinerator is 113190, expiration date 9/9/96. This permit will be automatically renewed for a 90 day conditional extension cycle to allow additional time to complete the stack test. The off-site facility currently being used is [REDACTED] which is licensed by the New York State Department of Environmental Conservation to destroy non-hazardous material under Permit No. 1-2820-01727/00010-0 (expiration date 06/23/2000).

A compliance statement signed by a high ranking company official from [REDACTED] indicating that the manufacture of the intermediate Ro 19-3052 will be in compliance with all local and national laws is included in Appendix B. The [REDACTED] plant has an incinerator on site which can treat at [REDACTED] of hazardous solid. A compliance statement signed by a high ranking company official indicating that the manufacture of the intermediate Ro 19-3052 will be in compliance with all local and national laws is included in Appendix B.

The Roche Basle and Sisseln plant has an incinerator on site which can treat hazardous solid waste. A certificate of compliance signed by a high ranking company official indicating that the production of Orlistat drug substance and milling of Orlistat drug substance will be in compliance with all local and national laws for Roche Basle and Roche Sisseln plant, respectively, is included in Appendix B.

No special method of disposal of waste by the end user is anticipated. United States' hospitals, pharmacies or clinics will dispose of empty or partially empty packages in accordance with applicable local, state and federal regulations. In home, 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, although minimal quantities of unused drug may be disposed of in the sewer system.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Proprietary Name: Xenical

Generic Name: Orlistat

Research Code: Ro 18-0647

Chemical Name: (S)-2-Formylamino-4-methyl-pentanoic acid (S)-1-
[(2S,3S)hexyl-4-oxo-oxetan-2-ylmethyl]-dodecyl ester
(= Orlistat)

CAS No: 96829-58-2

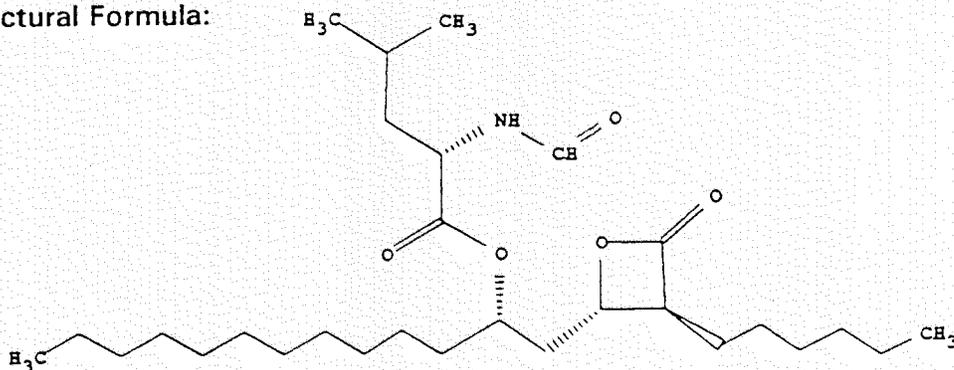
Empirical Formula: $C_{29}H_{53}NO_5$

Molecular Weight: 495.75

Melting Range: 42-44°C as per USP Method I

Physical Description: White to almost white powder

Structural Formula:



Additives:

The list of chemical substances associated with the manufacture of the drug product along with CAS No. and copies of available MSDSs are provided in confidential Appendix D.

Impurities:

There are no single impurities detected in the drug substance or the drug product that exceed more than 1% at the time of release.

The details of physical chemical property data and chemicals utilized in production of Xenical are provided as follows:

- Appendix A: It contains the physical chemical property data of Orlistat and Material Safety Data Sheet for the drug substance.
- Appendix C (confidential): It contains the list of chemical substances associated with the manufacture of the drug substance along with CAS Number and copies of available MSDSs for the raw materials utilized.
- Appendix D (confidential): The list of chemical substances associated with the manufacture of the drug product along with CAS Number and copies of available MSDSs are provided in confidential Appendix D.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

All manufacturing operations are carried out under carefully controlled conditions and in compliance with applicable environmental regulations of the countries in which the operations occur.

The general compliance information and annual production volume is provided as follows:

- Appendix B : Compliance statements signed by a high ranking company official from [REDACTED] F. Hoffmann-La Roche Ltd., Basle, Switzerland, Roche AG, Sisseln, Switzerland, [REDACTED] and Hoffmann-La Roche Inc., Nutley, New Jersey are included in it.
- Appendix E (confidential): It contains the information on the maximum projected annual use of Orlistat for the five-year period following introduction of Xenical.

Control of environmental emissions for the various manufacturing operations is outlined below:

6.1 Manufacture of the Intermediate Ro 19-3052 [REDACTED]

[REDACTED] is producing the [REDACTED] Ro 19-3052 under carefully controlled conditions and in compliance with relevant regulations. A compliance certificate signed by high ranking company official certifying that the manufacture of the [REDACTED] Ro 19-3052:

- will be in compliance with all local and national environmental laws
- will be in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
- that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws is included in Appendix B.

6.2 Manufacture of Intermediate Ro 19-3052 [REDACTED]

[REDACTED] is producing the intermediate Ro 19-3052 under carefully controlled conditions and in compliance with relevant [REDACTED] regulations, such as Ministerial Decree 203 of July 12, 1990. A compliance certificate signed by a high ranking

company official certifying that the manufacture of the intermediate Ro 19-3052:

- will be in compliance with all local and national environmental laws
- will be in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
- that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws is included in Appendix B.

6.3 Manufacture of the Orlistat drug Substance - F. Hoffmann-La Roche Ltd., Basle, Switzerland

Roche Basle plant in Switzerland is producing the drug substance under carefully controlled conditions and in compliance with the rules of Good Manufacturing Practices and the Swiss Environmental Protection Laws. A compliance certificate signed by a high ranking company official certifying that the production of Orlistat drug substance:

- will be in compliance with all local and national environmental laws
- will be in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
- that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws is included in Appendix B.

6.4 ██████████ of the Orlistat drug Substance - Roche AG, Sisseln, Switzerland

Roche AG Sisseln plant in Switzerland is ██████████ the drug substance under carefully controlled conditions and in compliance with the rules of Good Manufacturing Practices and the Swiss Environmental Protection Laws. A compliance certificate signed by a high ranking company official certifying that the milling of Orlistat drug substance:

- will be in compliance with all local and national environmental laws
- will be in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
- that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws is included in Appendix B.

6.5 [REDACTED] of the Orlistat drug Substance [REDACTED]
[REDACTED]

[REDACTED] plant in [REDACTED] the drug substance under carefully controlled conditions and in compliance with the rules of Good Manufacturing Practices and the [REDACTED] Environmental Protection Laws. A compliance certificate signed by a high ranking company official certifying that the [REDACTED] of Orlistat drug substance:

- will be in compliance with all local and national environmental laws
- will be in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
- that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws is included in Appendix B.

6.6 Xenical Drug Product Manufacture: Hoffmann-La Roche Inc., Nutley, New Jersey

The Xenical capsules, 60 mg and 120 mg, will be produced at the Hoffmann-La Roche Inc. plant in Nutley, New Jersey.

All manufacturing operations are carried out under carefully controlled conditions and in compliance with applicable environmental regulations of the United States Environmental Protection Agency (USEPA) and New Jersey Department of Environmental Protection and Energy (NJDEPE).

For the capsule manufacturing operation in Nutley, N. J. , we are providing both a compliance certification (in Appendix B) and a description below of expected emissions and controls.

Emissions of pollutants into the air and water and disposal of solid waste for the Hoffmann-La Roche Nutley facility are regulated to a high degree by the State of New Jersey, specifically in Title 7, Environmental Protection, of the New Jersey Administrative Code.

6.6.a Substances Expected to be Emitted

During the manufacturing process some material may be released in the following phases:

- **Air Phase (Air Emissions)** Air emissions consist of minor amounts of pharmaceutical dust (active ingredients plus excipients, Appendix D) lost during loading of [REDACTED] into the [REDACTED] and capsule manufacturing equipment.
- **Aqueous Phase (Wastewater Emission)** The wastewater from the Xenical capsule manufacturing process consists mainly of equipment washdowns. The wastewater from the blending and capsule operations contains residual amounts of active ingredients along with [REDACTED] used in the manufacture of the drug product (Appendix D).
- **Terrestrial Phase (Solid/Liquid Waste)** Solids for disposal consist mainly of [REDACTED] capsules, rejected capsules and unused product. Appendix D contains the list of excipients in the capsules.

The Orlistat drug substance and the excipients listed in Appendix D have potential for release in the air phase, aqueous phase and solid phase. However, very minute quantities are expected to be released during the capsules manufacturing and packaging operation.

6.6.b Controls Exercised

During the manufacture of Xenical capsules, the following control measures are utilized to minimize emissions in the [REDACTED]

- [REDACTED] (Air Emissions) Emission of particulate matter is controlled by means of [REDACTED] filter dust collectors, which enables the dust emissions to remain within the limits of New Jersey regulations. The various types of equipment used in the [REDACTED] operations for the production of Xenical are serviced by dust collectors, of the [REDACTED] filter type. The operating efficiency of [REDACTED] filter dust collectors is probably [REDACTED]. The level of dust in the processing areas during product blending and capsule manufacturing operations will be controlled by local exhaust ventilation and general room ventilation. In addition, employee exposure levels will be minimized by the use of personal protective equipment such as respiratory protectors, if required.
- [REDACTED] (Wastewater Emission) Wastewaters from the Xenical process are combined with wastewater from other manufacturing processes and discharged through a pretreatment system to the Passaic Valley Sewerage Commission (PVSC) treatment plant (a POTW).
- [REDACTED] (Solid/Liquid Waste) As mentioned under item 4e, the solid/liquid waste will be incinerated in an on site medical waste incinerator or incinerated by an off-site licensed commercial incinerator.

6.6.c Citation of and Statement of Compliance with Applicable Emission Requirements

The manufacturing of Xenical capsules will be in accordance with all applicable Federal, State and local emission requirements, including occupational health. The following are the regulatory requirements in New Jersey:

- **Air Emission Regulations and Permits** Air emissions in New Jersey are regulated under N.J.A.C. 7:26-1 et seq., the Bureau of Air Pollution Control portion of the New Jersey Administrative Code. These regulations include subchapters governing allowable emissions of particulate matter and volatile organic substances from manufacturing processes, as well as setting forth the requirements for obtaining permits to construct or alter process equipment. The [REDACTED] and its [REDACTED] collector are covered by NJDEPE certificate to operate number 102287 (expiration date October 10, 1998). The remaining particulate collection equipment predates the current permit system and is thus "grandfathered". All equipment operates in compliance with current requirements for particulate emissions.
- **Wastewater Emission Regulations and Permits** Wastewaters from the Xenical capsule process are combined with wastewater from other manufacturing processes and discharged through a pretreatment system to the Passaic Valley Sewerage Commission (PVSC) treatment plant (a POTW) under PVSC Permit Number 24402882 (expiration date April 14, 1996). The application to renew the permit has been already filed with the PVSC. The decision on the permit renewal application has not yet been made by the PVSC, the permit is automatically extended pending PVSC action. The State of New Jersey regulates the Roche/Nutley pretreatment facility as a significant industrial user and has issued non-contact cooling water and storm water discharge permit number NJ 0034185 (expiration date January 31, 2000) under the New Jersey Pollutant Discharge Elimination System (NJPDES) regulations.
- **Solid Emission Regulations and Permits** Disposal of solid waste and hazardous waste is controlled under the New Jersey Department of Environmental Protection and Energy (NJDEPE) regulations, N.J.A.C. 7:25-1 et seq. Disposal and processing of solid/liquid waste from the Xenical capsule manufacturing process will be in compliance with the NJDEPE waste regulations referenced above. The permit information is provided under item 4e.