CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-708

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND FINDING OF NO SIGNIFICANT IMPACT

FOR

Lupron Depot, 3-month, 11.25mg

Leuprolide Acetate for Depot Suspension

NDA 20-708

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division OF Reproductive and Urologic Drug Products

(HFD-580)

FINDING *OF NO* SIGNIFICANT IMPACT
NDA 20-708
Lupron Depot- 3 month, 11.25mg
Leuprolide acetate
For Depot Suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process. The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that 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 **Lupron Depot, 3-Month, 11.25mg, TAP Holdings Inc.,** has prepared an environmental assessment in accordance with 21 CFR 25.3la (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Leuprolide acetate is a chemically synthesized peptide drug which is administered as intramuscular injection every three months for the management of endometriosis and anemia caused by uterine fibroids. The drug substance will be manufactured by Abbott Laboratories, North Chicago, Illinois, USA, and Takeda Chemical Industries, Ltd, in Japan. The drug product will be manufactured by Takeda Chemical Industries Ltd at Osaka Plant and Shonan Plant in Japan, and may be tested and packaged for marketing by Abbott Laboratories, North Chicago, Illinois, USA. The finished drug product will be used in hospitals and clinics throughout the United states.

Leuprolide acetate, a peptide expected to have extremely low toxicity, is metabolized in vivo to inactive metabolites. Any excreted metabolites that enter public water and sewage treatment facilities are expected to be rapidly biodegraded by soil and water microbial organisms.

Off specification lots of bulk drug substance from Abbott's North Chicago facility will be treated as a special pharmaceutical waste and sent to an incineration site. Any unused drug product that is returned to Abbott will be also separated and will be treated as special pharmaceutical waste and sent an incinerator.

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.

1/28/97
DATE

PREPARED BY
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
HFD-820 Assigned to HFD-580

1/28/97
DATE

DIVISION CONCURRENCE
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
HFD-820 Assigned to HFD-580

2/1/97
DATE

CONCURRED
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Certification stating that EA is FOIable
Material safety Data Sheets for Drug Substances

cc:
Orig. NDA 20-708
HFD-580/Division File
HFD-580/MRhee/ADunson
R/D Init. By Rhee
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351 HFD-~~004~~/FONSI File
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NON-CONFIDENTIAL

Environmental Assessment of Lupron Depot® - 3 Month 11.25 mg

TAP Holdings Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

The Environmental Assessment (EA) being submitted by TAP Holdings Inc. on this product is a nonconfidential document and has appendices A, B, and C. These are: 1) Non-Confidential, Appendix A containing Material Safety Data Sheets (MSDS); 2) Non-Confidential, Appendix B containing references; and 3) Confidential, Appendix C which is the full EA for review by FDA.

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15-5 Certificate of Environmental Compliance for the Manufacture of Drug Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg), at Osaka Plant of Takeda Chemical Industries, Ltd. From the Managers of Environmental Pollution Control, Water Quality Control and Industrial Waste Guidance Departments, Osaka City Government, Japan

15-6 Certificate of Environmental Compliance from Plant General Manager of Osaka Plant for the Manufacture of Drug Product, and Vehicle (Lupron Depot® - 3 Month, 11.25 mg)

15-7 Certificate of Environmental Compliance from the Mayor of Fujisawa City for the Manufacture of Drug Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg)

15-8 Certificate of Environmental Compliance from the Director of Shonan Plant, Fujisawa City, Japan

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1 **DATE**

April 30 ,1996

2 **NAME OF APPLICANT**

TAP Holdings Inc.

3 **ADDRESS**

Bannockburn Lake Office Plaza

2355 Waukegan Road

Deerfield, Illinois 60015

4 **DESCRIPTION OF THE PROPOSED ACTION**

4.1 REQUESTED APPROVAL

TAP Holdings Inc. is seeking an approval through this New Drug Application (NDA 20-708) for the manufacture, packaging, and distribution of Lupron Depot®-3 Month 11.25 mg, for the management of endometriosis and anemia caused by uterine fibroids, pursuant to Section 505(b) of the Food, Drug, and Cosmetic Act. The drug product is a leuprolide acetate suspension designated for one intramuscular injection, every three months containing 11.25 mg of the active ingredient, leuprolide acetate (also referred to in the Environmental Assessment as leuprolide). This dosage form consists of leuprolide acetate enveloped in a polymer comprised of polylactic acid. The drug-polymer microspheres are mixed at the time of use with a sterile diluent and the resulting suspension is injected intramuscularly, providing 3 months of sustained leuprolide release into the tissue.

The drug product is administered with the help of an administration kit that includes: 1) a single dose glass vial containing the drug product which is the biodegradable

3-month depot comprising sterile, white, and odorless formulated microspheres [designated TAP-144-SR (3M)(11.25 mg)] containing leuprolide acetate (11.25 mg), polylactic acid (**** mg), and D-mannitol (***** mg); 2) a glass ampule containing the diluent which is clear, colorless, and slightly viscous liquid [designated TAP-144-SR(3M) Vehicle] for reconstitution; 3) one polypropylene syringe with 23 Gauge Needle for withdrawing the vehicle from the glass ampule and placing it in the vial containing the drug product; and 4) one 23 Gauge Needle used along with the syringe for intravenous injection. The administration kit is packaged in a polystyrene, Amoco resin 4400E container.

A five year forecast for the quantity of the drug substance that will be required to manufacture the drug product Lupron Depot® from 1997 (********) to 2001 (*******) is presented in Confidential Apppendix C.

The bulk drug, leuprolide acetate, manufactured by Abbott Laboratories has been the subject of a first and previously approved new drug application (NDA 19-010, approved April 9, 1985) for Lupron® Injection, list 3626. Subsequently, the following NDAs have also been approved:

Lupron Depot® 7.5 mg, list 3629 (NDA 19-372 in January 1988)

Lupron Depot® 3.75 mg, list 3639 (NDA 20-011 in October 1990)

Lupron Depot®-PED 11.25 mg, list 2270 (NDA 20-263 in April 1993)

Lupron Depot® 3.75 mg, list 3639 (NDA 19-943 in March 1995)

Lupron Depot® - 3 Month 22.5 mg, list 3336 (NDA 20-517 in December 1995).

The format of the EA for Lupron Depot®-3 Month, 11.25 mg, is arranged as required in 21 CFR 25.31a "Environmental Assessment for Proposed Approvals of

FDA-regulated Products", and "Guidance for the Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements" provided in the document from Center for Drug Evaluations Research (CDER) of FDA (1995). As recommended in this FDA, CDER guidance document and based on the estimated Expected Introduction Concentration (EIC) of ********** which is several orders of magnitude below the one (1) part per billion (1 ppb) limit set in the guidance document, and the fact that leuprolide acetate, being a peptide is readily biodegradable to CO_2, an abbreviated Enviromental Assessment (EA), excluding items 7-11 is presented.

Supporting documents for the items discussed in this non-confidential non-confidential EA have been organized as attachments to this non-confidential document, as well as Appendices A (Non-Confidential; Material Safety Data Sheets), B (Non-Confidential, References), and C Confidential (EA).

4.2 NEED FOR ACTION

Leuprolide acetate is a long-acting GnRH analog. It is a nonapeptide synthesized sequentially in solution using the classical method of blocking, compiling, and deblocking of the aminoacids. All the aminoacids are levo-rotatory (L-) except for the leucine in the sixth position which is dextro-rotatary (D-) (Confidential Appendix C). Administration of leuprolide acetate results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing results in decreased secretion of gonadal steroids. Consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible through discontinuation of drug therapy. Leuprolide acetate is not active when given orally. However, the intramuscular injection of the biodegradable Lupron Depot® formulation provides 3 months of sustained leuprolide

release into the tissue. The subject of this NDA and the Environmental Assessment prepared in this document is Lupron Depot®-3 Month, 11.25 mg, which will be used for the management of endometriosis and anemia caused by uterine fibroids.

4.3 PRODUCTION LOCATIONS AND THEIR ENVIRONMENTAL SETTINGS

The bulk drug, leuprolide acetate, is manufactured by Abbott Laboratories and is the subject of a previously approved New Drug Application (19-010, approved April 10, 1985). Abbott Laboratories, North Chicago, USA will be the primary supplier of the bulk drug substance. Takeda Chemical Industries Ltd., Japan is an alternate bulk drug supplier. The bulk drug is shipped from Abbott Laboratories to Takeda Chemical Industries, Ltd., Japan, for manufacture of the final dosage form. Both the drug product (microspheres) and diluent are manufactured by Takeda Chemical Industries, Ltd., Japan, from where they are packaged in the primary containers and shipped to Abbott Laboratories, USA for labeling and final packaging. The sites of manufacture of bulk drug and the drug product and the diluents, as well as the packaging (Figure 4-1) are listed below along with their addresses. The drug is distributed within the United States by TAP Pharmaceuticals Inc., Bannockburn Lake Office Plaza, 2355. Waukegan Road, Deerfield, Illinois 60015, USA

A brief description of the environments at and adjacent to the manufacturing and packaging facilities involved in the drug substance and the drug product manufacture and packaging of drug product are provided after the listing of the production locations.

4.3.1 Synthesis and Production of Bulk Drug Substance

The synthesis scheme of leuprolide acetate powder is described in Confidential

Apppendix C. Production of the bulk drug substance, leuprolide acetate is conducted at the following locations:

1. Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois, 60064, USA (Primary Location)

2. Takeda Chemical Industries, Ltd., 4720 Mitsui, Hikari Plant, Hikari-City, Yamaguchi, Prefecture, Japan (Alternate Location)

4.3.2 Manufacture of the Final Dosage Form (Drug Product and Diluent)

1. Takeda Chemical Industries Ltd., 17-85 Juso Honmachi, 2-chome, Yodogawaku, Osaka Plant, Osaka City, Japan.

2. Takeda Chemical Industries Ltd., 2-26-1 Muraoka Higashi, Shonan Plant, Fujisawa City, Kanagawa, Japan.

4.3.3 Packaging of the Final Dosage Form (Drug Product and Diluent)

1. Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois, 60064, USA

4.3.4 Takeda Chemical Industries, Ltd., Hikari City, Japan

The manufacturing of drug substance, leuprolide acetate, is conducted at the Hikari Plant of Takeda Chemical Industries Ltd. located in the center of Hikari City, Yamaguchi Prefecture, Japan as an alterante source. The southern part of Hikari Plant is bordered by the Seto Inland National Park, and the northern side is adjacent to a commercial and residential area. The Hikari plant has a total area of about 0.37 square miles. The climate of Hikari City is characterized by warm summers (71 to 95°F) and cold to moderate winters (28 to 55°F) The average annual rainfall is 67 inches. Most industries and residences in

Hikari City obtain potable water from the City of Hikari municipal water supply. The source of the municipal water supply is the Shimata river, which passes from the Hikari City from north to south and flows down into Seto Inland Sea. The Hiakri Plant uses municipal water only. Wastewater is sewered to an on site water treatment facility.

4.3.5 Takeda Chemical Industries, Osaka City, Japan

The method of manufacture of the drug product, Lupron Depot®, 3 month, 11.25 mg [TAP-144-SR(3M) Injection (11.25 mg)] is described in the Confidential Appendix C. The Osaka plant of the Takeda Chemical Industries, Ltd. is the site of drug product, leuprolide manufacture and is located in the northwestern part of Osaka City. It is situated approximately 650 yards from the Yodo river and is more than 0.07 square miles in area. Drainage is dominantly to the south toward the river. The climate of Osaka City is characterized by warm summers (75 to 95°F) and cold to moderate winters (36 to 50°F). The average rainfall is 52 inches. Most industries and residences in Osaka City obtain potable water from the City of Osaka municipal water supply. The source of municipal water supply is the Yodo River flowing from Lake Biwa. The Osaka Plant uses municipal water only. Wastewater is sewered to an on site water treatment facility.

4.3.6 Takeda Chemical Industries, Fujisawa City, Japan

The method of maufacture of drug product and the vehicle at Shonan Plant of the Takeda Chemical Industries, Ltd. located at the Fujisawa City is described in Confidential Appendix C. Most industries and residences in Fujisawa City obtain potable water from the City of Fujisawa municipal water supply. The source of municipal water supply is the Sagami

River flowing from Lake Sagami. The Shonan Plant uses municipal water only. Wastewater is sewered to an onsite water treatment facility.

4.3.7 Abbott Laboratories, North Chicago

The synthesis of bulk drug (Confidential Appendix C) and the packaging of final dosage form (drug product and vehicle) is conducted at Abbott Laboratories, North Chicago, USA. The properties of the Abbott Laboratories are located within Lake County, Illinois. The North Chicago property lies 600 to 1000 feet west of Lake Michigan at an elevation of ten to fifteen feet above the average 580 foot mean sea level elevation of the lake. There are no other significant geographic features, such as mountains, lakes (aside from Lake Michigan) or rivers in proximity to the manufacturing site. The area is topographically flat and slopes very gently to the east, toward Lake Michigan. Drainage is dominantly to the east-southeast, again toward the lake. The climate of northeastern Illinois is characterized by warm summers (74 to 94°F) and cold winters (20 to 32°F). The average annual rainfall is 32 inches; wind directions are highly variable.

Most industries and residences near the Abbott, North Chicago facility are served by the City of North Chicago municipal water supply. The source of the municipal water supply is Lake Michigan. The Abbott North Chicago facility currently uses municipal water. Wastewater is sewered to the treatment facility of the North Shore Sanitary District. Land use (zoning) near the North Chicago facility is primarily residential and industrial. The portion of Lake County in which it is located is part of the Chicago metropolitan area.

The physiographic features and near surface deposits of northeastern Illinois are the result of the late Pleistocene Wisconsonian glaciation, the most recent of four episodes of

continental glaciation. Glacial deposits of the Lake County area consist of lake sediments (clay, silt and sand) of the Equality Formation, and clayey to silty glacial till of the Lake Border Morainic System. From 50 to 200 feet of Pleistocene glacial sediments unconformably overlie Silurian dolomite in this area. The Paleozoic stratigraphic section in this area from top to bottom includes Silurian dolomite, Ordovician shale, dolomite. and sandstone, and Cambrian sandstone. The Paleozoic section unconformably overlies Precambrian crystalline rocks. Three dominant aquifer systems, the Basal Bedrock, Midwest Bedrock, and Upper Bedrock, underlie northeastern Illinois. Principal water producing zones include sandstone of the Eau Claire and Mount Simon Formations for the Basal Bedrock system, the Ironton-Galesville and Glenwood-St. Peter (Ancell aquifer) sandstones for the Midwest Bedrock System, and the Silurian Dolomite aquifer for the Upper Bedrock system. Locally, Pleistocene deposits may yield large quantities of water (greater than 1000 gpm); however, development of this aquifer is limited. Municipal and industrial water wells in the Chicago region tap the deeper aquifer systems.

4.4 LOCATIONS OF USE

The Lupron Depot®-3 Month 11.25 mg, will be administered under the direction of physicians to patients afflicted with endometriosis or anemia caused by uterine fibroids. The locations of use are, therefore, mainly hospitals and clinics throughout the United States.

4.5 DISPOSAL SITES

Leuprolide acetate is metabolized extensively in the human body. The

excipients used in the drug product, as well as the components of the diluent are easily biodegradable. Negligible quantities of the drug substance and its metabolites or excipients are excreted by patients which will enter municipal treatment systems through domestic sewage.

Off specification lots of bulk drug substance from Abbott's North Chicago facility will be treated as a special pharmaceutical waste and sent to an incineration site. Any unused drug product that is returned to Abbott (beyond expiration date) will be separated; the vials with drug will be treated as special pharmaceutical waste and sent to an incinerator. All other components are sent to a landfill. Details of mode of disposal of wastes are discussed in Section 6.0.

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

Information on the drug substance, leuprolide acetate, is provided below to allow for accurate location of data about the chemical in scientific literature and to allow for identification of closely related compounds. The information is taken from the Chemistry and Manufacturing Controls Section of the NDA 20-708.

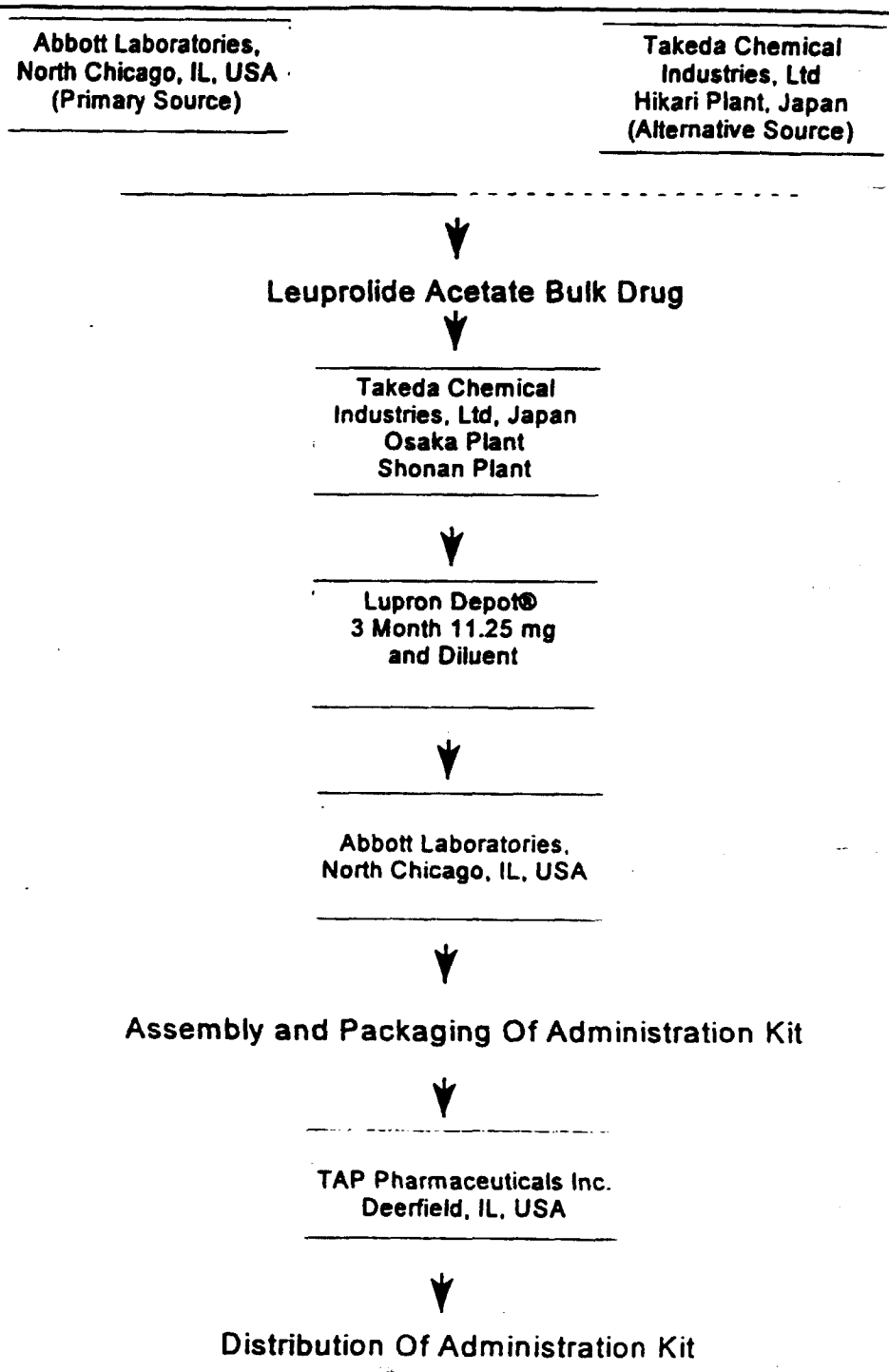


Figure 4-1
Sites Relevant to the Manufacture,
Packaging, and Distribution of Lupron Depot® -
3 Month 11.25 mg

5.1 NOMENCLATURE

5.1.1 Established Name (United States Adopted Name - USAN)

Leuprolide Acetate

5.1.2 Brand or Proprietary Name

Lupron Depot® - 3 Month 11.25

5.1.3 Chemical Abstracts Name

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide

5.1.4 CAS Registry Number

74381-53-6

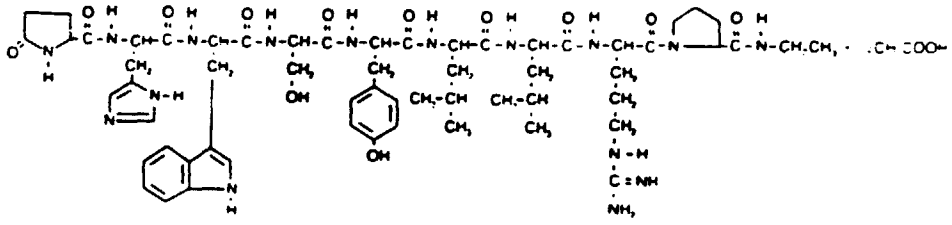
5.1.5 Laboratory Codes

Abbott-43818/Takeda-TAP-144

5.1.6 Molecular Formula and Weight

Formula - $C_{59}H_{84}N_{16}O_{12}.CH_3COOH$; Weight - 1269.47

5.1.7 Structural (Graphic) Formula



5.1.8 Dissociation Constant and K_{ow}

Three ionization sites are present: imidazolyl nitrogen of histidine, pKa 6.0; the phenolic hydroxyl of tyrosine pKa 10.0; and the guanidine nitrogen of arginine pKa 13.0; log K_{ow} 0.52 to 0.98 (Abbott Laboratories Report R&D/92/143, 1992; Confidential Appendix C).

5.1.9 Physical Description

White Powder

5.2 ADDITIVES

The excipients of the drug product and the vehicle are listed in Tables 5-1 and 5-2, respectively. As seen from the table, most of the components are readily biodegradable.

Table 5-1

Composition of Lupron Depot®-3 Month 11.25 mg [TAP-144-SR(3M) 11.25 mg]

Ingredient	Per Vial
Leuprolide Acetate	*****
Polylactic Acid	*****
D-Mannitol	*****
Total	*****

Table 5-2

Composition of the Vehicle (TAP-144-SR(3M)Vehicle)

Ingredient	Per Ampule	Per Use
D-Mannitol	***	***
Carboxy Methyl-Cellulose - sodium	***	***
Polysorbate 80	***	***
Glacial Acetic Acid	—	—
Appropriate amount if needed to adjust pH		
Water for Injection	***	***

5.3 IMPURITIES

Approximately 5 impurities i.e., [des-Leu^{7}]TAP-144 (<0.1%); unknown (<0.1); TAP-144, modified (0,.45%); [des-ProNHEt^{9}]TAP-144 (<0.1%); and [N^{G}-AC-Arg^{8}]-TAP-144 (<0.1%) have been identified (Adjei and Hsu, 1993; Appendix B) and total amount of the five impurities combined did not exceed 1% and, therefore, further elaboration of these impurities have not been made in the EA, as per CDER, FDA (1995) guidance document (1993).

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

This section discusses the introduction of the substances into the environment and the controls exercised during the manufacturing and packaging operations. The

manufacturing facilities of Takeda Chemical Industries Ltd, in Hikari, Osaka and Fujisawa cities in Japan are governed by the Environmental Laws and Regulations of Japan (Attachment 15-1). The manufacturing of bulk drug and the packaging operations for the drug product at Abbott Laboratories, North Chicago are governed by Environmental Laws and Regulations promulgated under the National Environmental Policy Act (NEPA).

6.1 Synthesis and Production of Bulk Drug Substance at Abbott Laboratories, North Chicago, Illinois, USA (Primary Location)

6.1.1 Substances Expected to be Emitted

Atmospheric Emissions

The Abbott facility at North Chicago is equipped with Air Pollution Controls. The drug substance will be manufactured in a closed system. Particulate emissions will be negligible as the synthesis of leuprolide acetate involves the use of a variety of solvents as seen from the Confidential Appendix C. An examination of the details of synthesis shows that the most likely volatiles emitted will be acetone, acetic acid and alcohol. The only potential exposure to the air could be during the dispensing of the bulk drug for export to Japan, which is also conducted carefully in specially packed containers which are housed in drums.

Aqueous Wastes

Losses during formulation as aqueous waste are insignificant since the total quantity of the drug substance produced for this indication will be ******* (******). These very small amounts are deactivated and then sewered. If any significant amount of drug substance is left in the process tanks, it will be contained and disposed of as a special

pharmaceutical waste. Any final synthesis waste such as intermediates during the synthesis process will also be disposed of as a special pharmaceutical waste. Wastewater from equipment and room cleaning is directed to the chemical sewer which goes to the Abbott North Chicago Wastewater Treatment Plant. After pre-treatment at Abbott, North Chicago, the wastewater is discharged [Abbott Wastewater Discharge Control Document (Permit) No. 95-5A] to the sewer system of the North Shore Sanitary District (NSSD) and from there to Gurnee Wastewater Treatment Plant of the NSSD. The other waste streams (eg., solvents) some with water are: 1) recovered; 2) recycled; 3) incinerated; or 4) used as a boiler fuel.

Solid Wastes

Solid wastes from manufacturing of bulk drug as leuprolide acetate are expected to be minimal since the peak yearly production of the drug substance for this indication is *******. Packaging rejects, air filter cartridges, and protective clothing worn by employees will be collected in drums and disposed of off-site. These solid wastes will be transported to Waste Management of Wisconsin, Bristol, Wisconsin (Permit No. 3062). Unused drug substance, past expiration date will be disposed of as a special pharmaceutical waste, and incinerated using the contractors listed in Table 6-1.

6.1.2 Controls Exercised on Residuals and Emissions

Air emissions are controlled as required by the Operating Permit of the Illinois Environmental Protection Agency (IEPA). Record of emissions are maintained and available for inspection. All air emissions are within the permitted limits. Solid wastes are disposed of at permitted waste facilities. Wastes are sent for recycling into fuels at the waste facilities discussed in Table 6-1. Wastes are sent for recyling into fuels atthe waste facilities

discussed in Table 6-1. Special Pharmaceutical wastes discussed above are sent for incineration (Table 6-1).

6.1.3 Compliance of Proposed Action with Applicable Emission Requirements

Since particulate and VOC emissions are insignificant [Illinois EPA (IEPA) Definition: less than 0.1 lb./hr. and 0.44 tons per year], at North Chicago facility, manufacturing of less than ******* of bulk drug will be in compliance with IEPA requirements.

Only tank residuals and fill line residuals will be sewered. In the event some amount of drug substance is left in the process tanks for disposal, it will be drummed up and disposed of as a special pharmaceutical waste. Particulate emissions from the drug substance manufacturing facility at Abbott, North Chicago is regulated under a permit issued by the Illinois Environmental Protection Agency. Wastewater from manufacturing must meet the General Pretreatment Standards in 40 CFR Part 403 and the Effluent Guidelines and standards for Pharmaceutical Manufacturing in 40 CFR Part 439. The prohibitions and limitations for discharge into the sewer system of the North Shore Sanitary District (NSSD) are listed in NSSD Wastewater Discharge Control Document No. 95-5A. Solid wastes will be landfilled by Waste Management of Wisconsin under Permit No. 3062 from the State of Wisconsin. Department of Natural Resources.

A Certifice of General Environmental Compliance with applicable emission requirements for the manufacture of drug at Abbott, North Chicago is provided in Attachment 15-2.

6.1.4 Effect of the Proposed Action on Compliance with Current Emission Requirements

Emissions and releases from the manufacture of drug substance will not exceed the limitations of current permits. Manufacturing of this product will be scheduled to fit within the existing framework of activities for which current emission requirements are applicable. No additional facilities are required to facilitate the manufacture of bulk drug for this indication.

6.2 Packaging of the Final Dosage Form at Abbott Laboratories, North Chicago, Illinois, USA

Unused administration kits, or those kits past expiration dates will be returned to Abbott Laboratories, North Chicago, where the drug product and the diluent, syringes and needles will be sorted out. Vials with the drug are treated as special waste and put in fiber or plastic drums and are sent for incineration at approved medical waste incinerators (Table 6-1). All other components of the kit are shredded in garbage hopper and treated as non-hazardous solid waste and go to the landfill managed by Waste Management of Wisconsin.

6.3 Synthesis of Bulk Drug, Leuprolide Acetate at Takeda Chemical Industries, Ltd., Hikari Plant, Hikari City, Japan

A certificate of compliance of Hikari Plant with local and national environmental regulations for the synthesis of bulk drug, leuprolide acetate by the Director of

Table 6-1

Waste Disposal Contractors and USEPA Registration*

Contractor	USEPA ID#	Function
		Incineration
		Fuels
		Solid Wastes

*This is a current list of contractors and is subject to change.

Environmental Protection Division, Environmental Protection and Public Health Department, Yamaguchi Perfectural Government, Japan is provided in the Attachment 15-3. As required by the FDA. CDER (1995), EA guidelines for those manufacturing sites located outside the United States, a letter from the General Manager of Hikari City Plant certifying that the facility is in compliance with all local and National regulations is provided in Attachment 15-4.

6.4 Manufacture of Drug Product and Diluent at Takeda Chemical Industries, Ltd., Osaka Plant, Osaka City, Japan

A certificate of compliance of Hikari Plant with local and national environmental regulations for the manufacture of Lupron Depot® (Drug Product and Diluent) by the Manager of Environmental Pollution Control Water Quality Control and Industrial Waste Guidance Departments, Osaka City Government, Japan is provided in the Attachment

15-5. As required by the FDA, CDER (1995), EA guidelines for those manufacturing sites located outside the United States, a letter from the General Manager of Osaka City Plant certifying that the facility is in compliance with all local and National regulations is provided in Attachment 15-6.

6.5 Manufacture of Drug Product and Diluent at Takeda Chemical Industries, Shonan Plant, Fujisawa City, Japan

A certificate of compliance of Shonan Plant with local and national environmental regulations for the manufacture of Lupron Depot® (Drug Product and Diluent) by the Mayor of Fujisawa City is provided in the Attachment 15-7. As required by the FDA, CDER (1995), EA guidelines for those manufacturing sites located outside the United States, a letter from the General Manager of Shonan Plant certifying that the facility is in compliance with all local and National regulations is provided in Attachment 15-8.

6.6 OCCUPATIONAL SAFETY

At the Abbott, North Chicago facility, chemicals used in manufacture of the drug substance, leuprolide acetate, are regulated by the Occupational Safety and Health Administration. Employees are trained in the proper operation of equipment in order to minimize potential safety, health and environmental risks. Extensive safety training is mandated, and Material Safety Data Sheets (Appendix A) are available to personnel for chemicals handled in the manufacturing area. Employee training is conducted on the chemical hazards associated with manufacturing.

Specified personal protective equipment (e.g., gloves, safety shoes, eye protection, respirators, etc.) and engineering controls designed for the equipment (e.g.,

exhausts to remove dust) are adequate to protect the employees. Specific procedures for gowning and degowning and spill containment are in place and all employees working in Abbott's leuprolide acetate manufacturing facility are trained to follow these procedures.

The safe transport of all drug-related materials is ensured by following protocols which include formal qualification of vendors, training of personnel, and rigid specification of containers and materials. Access to drug substance is restricted to authorized personnel.

6.7 AMOUNT OF SUBSTANCES ENTERING THE ENVIRONMENT

Human drugs find their way into the environmental compartments (eg. soil, air, water) through manufacture, use, disposal and accidental spills. The two major sources of environmental exposure of the drug are: 1) the patients who use the drug product; the drug product and/or its metabolites are discharged into the domestic sewer through excreta of the patients; and 2) release of the drug or its precursors or by-products through wastewater from the manufacturing plants. In either case the municipal sewage in the wastewater treatment plant could be the main recipient of these contaminant sources. The concentrations and releases in the subsections below are estimated without taking into consideration any degradation of the drug or its products at the manufacturing plants or during transport in the municipal sewage to the wastewater treatment plant (WTP), and, therefore, are worst case scenarios.

6.3.1 Human Elimination

The drug product, Lupron® Mist Depot®-3 Month 11.25 mg, is administered as intramuscular injection. Overa 3-month period susttained release of leuprolide acetate, the active ingredient, is facilitated. As it is released and metabolized within the human body, the drug product is biodegraded. Information available on the metabolism in the human body is provided below to understand the products that are eliminated (or excreted) from patients using this drug.

Leuprolide acetate (TAP-144) has mostly naturally occurring amino acids comprising in its structure (5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-arginyl-N-ethyl-L-prolinamide) with the exception of D-leucine. Amino acids that are naturally occurring can be metabolized by microbes to CO_2. Naeshiro et al (1990) used carbon-14 labeled leuprolide to study its metabolism in rats and dogs (Appendix B). Biotransformation of leuprolide in rats and dogs is consistent with what might be expected for a small peptide i.e., it involves the hydrolysis of amide bonds, followed by the excretion of smaller peptides in urine or bile and/or further catabolism of component amino acids. The metabolic pathways of leuprolide are summarized in Figure 6-1. Leuprolide is metabolized in rats and dogs through hydrolysis to form the M-I pentapeptide (Tyr-D-Leu-Leu-Arg-N-ethyl-prolinamide) and the M-III tripeptide (Tyr-D-Leu-Leu-OH). Further hydrolysis of M-I leads to the M-II tripeptide (Tyr-D-Leu-Leu-OH), while M-III is hydrolyzed to M-IV dipeptide (5-oxo-Pro-His-OH). Some of the metabolites are further catabolized as evidenced by the loss of label in the expired air and/or the apparent incorporation of carbon-14 into methanol-insoluble components in tissues. Naeshiro et al (1990) also demonstrated that most natural

amino acids could metabolize to $^{14}CO_2$, unless they are unnatural amino acids, such as D-leucine present in leuprolide acetate. For example, when leuprolide was labeled with carbon-14 in the oxo-proline moiety, about half the label was eliminated in the expired air, presumably after having been completely catabolized to $^{14}CO_2$. Labelling in the D-leucine, which is the only unnatural amino acid in the leuprolide molecule, afforded the retention of the label but some radioactivity was still eliminated in the expired air. Leuprolide labeled with carbon-14 in the oxo-proline moiety metabolized and approximately 47% was eliminated in the expired air ($^{14}CO_2$), and 49% of ^{14}C was excreted in urine (49%), only 1% was recovered in feces during a four day study period. In urine, the unchanged leuprolide accounted for 12% of the ^{14}C-dose, while M-III, a tripeptide form the amino side of the molecule (5-oxo-Pro-His-Trp-OH) represented 10% and M-IV, a dipeptide (5-oxo-Pro-His-OH) accounted for 17% of the dose. The metabolites of leuprolide do not contribute to the pharmacological activity of the compound nor the metabolism of leuprolide shown to be of any safety concern.

In patients given three 1 month depot injections of **** mg/dose at 4 week intervals, the urinary recoveries of leuprolide and its M-I metabolite averaged 1.2% and 0.4%, respectively, within 24 hours after the first dose and increased to 2.9% and 1.5% after 27 days. Based on these results it can be concluded that leuprolide is metabolized extensively in the human body, possibly leading to ultimate degradation to $^{14}CO_2$, which may be released in the expired air. Since CO_2 is a natural component of air, this expired air has no environmental impact. The components of the drug product such as poylactic acid and D-manitol are readily biodegradable to CO_2 and H_2O (Literature Review on the Polymers of Lactic and Glycolic Acid. Reference 5. Appendix B).

For the estimations of Expected Introduction Concentration (EIC) from use, it is assumed that all the drug forecasted for production in the United States (Confidential Appendix C), which is approximately ********** in a peak production year, will be ingested and eliminated by the U.S. population. This worst case estimate also assumes that there will be no metabolism of leuprolide acetate in the human body and that there will be no degradation in the domestic sewage receiving human excreta containing the drug product.

Typical minimum and maximum flow rates for wastewater treatment systems are set by Federal and State agencies to range from 280 to 1,500 L/person/day (Metcalf & Eddy, Inc., 1979). The 1990 Census gives the population of the United States as 250,378,000. The worst case concentration of the drug expected to be found in WTP is estimated from the dilution of the total drug produced in the year of maximum production (********) in the total wastewater produced in the United States.

The Expected Introduction Concentration (EIC) from use at the WTP can be estimated from the following equation:

$$EIC = \frac{Total\ drug\ produced\ (fifth\ year\ production)}{Total\ waste\ water\ in\ the\ United\ States}$$

Total leuprolide acetate produced [peak year (1998) production estimate] = **********

Total wastewater produced in the United States per year:

Liters of waste water per person = 280 L/day

Population of the United States = 250 million

Days in a year = 365 days

= 280 x 250 million x 365 = Liters of total waste water per year

Therefore the EIC for leuprolide acetate at the WTP will be:

$$\frac{****x\ 10^{9}}{280\ x\ 250\ x\ 10^{6}\ x\ 365} = **** \mu g/L\ (ppb) = {}^{or\ ****\ parts}_{per\ trillion\ (ppt)}$$

An equivalent method for calculating the concentration of drug that would be expected at the WTP is given in Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA (PMA, 1991) which estimates the EIC in ppm as follows:

$$ppm = (A)\ (B)\ (C)\ (D)\ (E)\ (F)$$

A = pounds/year production

B = year/365 days

C = day person/280 L (74 gallons)

D = 1/250 million persons

E = gallons/8.34 pounds

F = one million (x 10^6 = ppb)

Leuprolide acetate at WTP in ppb = ********** (A) x 1/365 (B) x 1/74 (C) x 1/(250 x 10^6) (D) x 1/8.34 (E) x 10^{19} (F) = **********

A method for calculating the expected introduction concentration (EIC) of the drug at the WTP is given in "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" published by the Center for Drug Evaluation Research (CDER), FDA, in November 1995 (FDA 1995). The estimate of the EIC in ppm based on this method is as follows.

EIC-Aquatic (ppm) = (A) (B) (C) (D) A = Kg/year production

B = 1 Liters per day entering WTP

C = years/365 days

D = 10^6 mg/Kg (conversion factor)

EIC of leuprolide acetate at WTP in ppm = ***** (A) x 1/1.115 x 10^{11} (B) x 1/365 (C) x 10^6 (D) = ********** or ********* .

The worst case EIC estimation for leuprolide in WTP calculated three different ways ranges from ***** to ***** ppt. This is several orders below the 1 ppb cutoff limit suggested in the FDA CDER (1995) EA guidelines.

6.5.2 Expected Introduction Concentration from Disposal

Synthesis of the drug substance and packaging of drug product is conducted at Abbott Laboratories, North Chicago, USA. Manufacture of the drug product is conducted in Japan. No air emissions are expected during synthesis or packaging at Abbott North Chicago. Less than 0.1% of the kit ingredients (other than the drug product) may be disposed of in the landfill as part of unused, rejected or expired drug product. Th drug product is itseslf incinerated. Thus, emissions from introduction into the environment through dispiosal would be negligible and no environmental impact is anticipted.

Figure 3. Metabolic Pathways for Leuprolide (TAP-144).

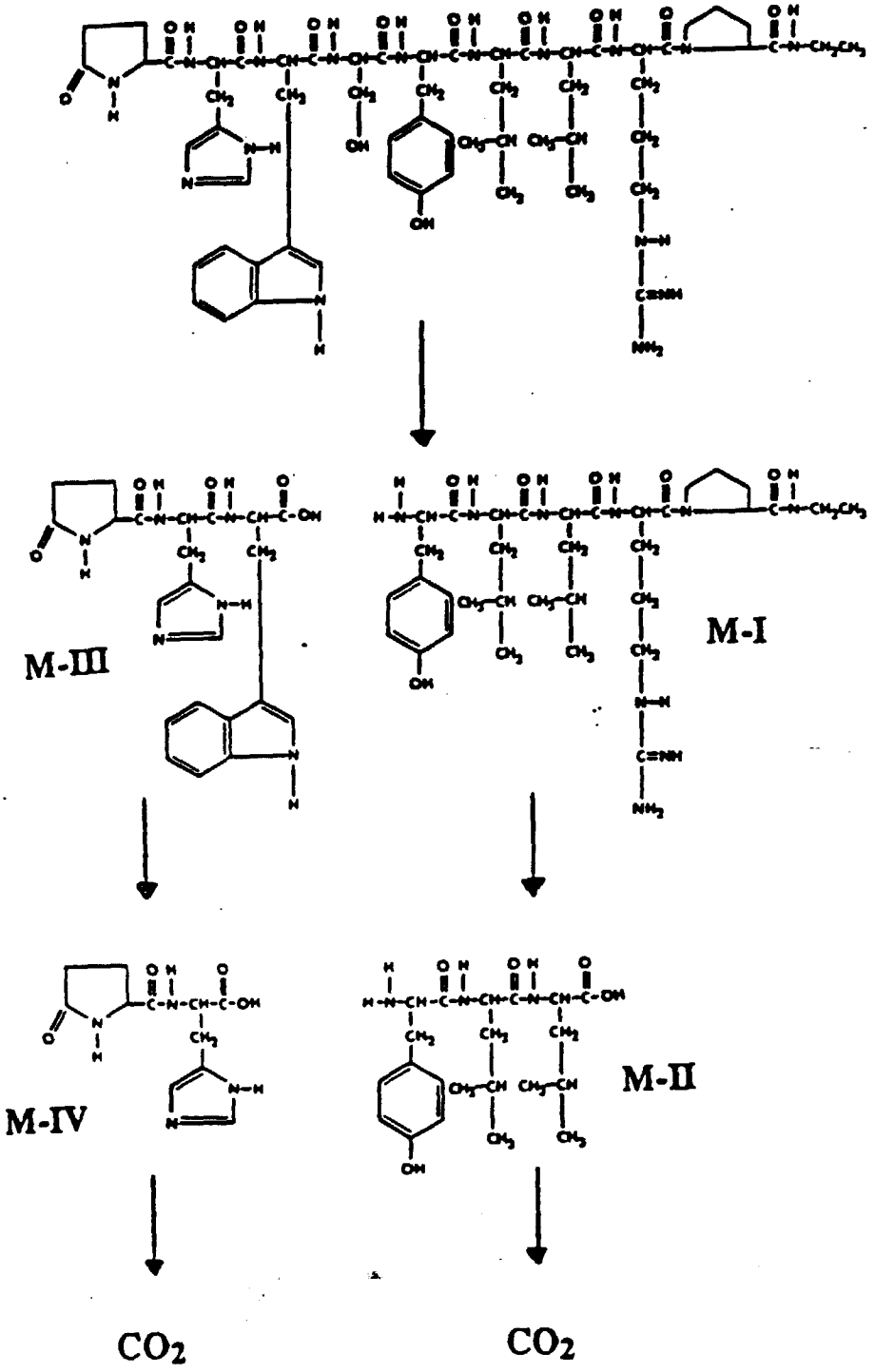


Figure 6-1
Proposed Pathway of Leuprolide Metabolism
32

7 FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The environmental fate of the emitted substances is not presented because the worst case EIC for the drug is less than *******. This is several orders below the cutoff limit of 1 ppb suggested by FDA, CDER (1995).

8 EFFECT OF EMITTED SUBSTANCES IN THE ENVIRONMENT

See Section 7.

9 USE OF RESOURCES AND ENERGY

See Section 7.

10 MITIGATION MEASURES

See Section 7.

11 ALTERNATIVES TO THE PROPOSED ACTION

See Section 7.

12 PREPARERS

Ranga Valagaleti, Ph.D
Director
Environmental Fate and Assessment Division
Analytical Biochemistry Laboratories, Inc.
7200 East ABC Lane
Columbia, Missouri 65202

The undersigned certify that the information presented is true, accurate, and complete for preparation of the Environmental Assessment Report in accordance with 21 CFR 25.31(a).

Signature Ranga Valagaleti Date 4-19-96

Title Director, Environmental Fate and Assessment

13 CERTIFICATION

The undersigned official certifies that the information presented herein and provided to Ranga Velagaleti by TAP Holdings Inc. (applicant) is true, accurate, and complete to the best of our knowledge.

The undersigned official certifies that this EA summary document and Appendices A and B contain non-confidential information and acknowledges that the non-confidential information will be made available to the public in accordance with 40 CFR part 1506.6.

Signature _____ Date 4/29/96

Title Regulatory Products Manager

14 REFERENCES

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2. Metcalf & Eddy, Inc., 1979. Wastewater Engineering: Treatment, Disposal, Reuse. Revised by G. Tchobanoglous. New York: McGraw-Hill Book Company.

3. Naeshiro, S.K., Mitani, S., Yoshida, K., Kobahashi, H., Kimura, T., Shimomura, S. and Tanayaura, S. 1990. Metabolic Fate of TAP-144, An LH-RH Agonist in Rats and Dogs. Japanese Journal of Therapeutics 18: 35-56.

4. Pharmaceutical Manufacturers Association (PMA). 1991. Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. Washington, D.C., July 1991. *Reference not included.

5. U.S. Food and Drug Administration. 1995. Guidance for the Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation Research, (CDER). FDA, Washington, D.C. *Reference not included.

6. Literature Review of the Polymers of Lactic and Glycolic Acids.

15 ATTACHMENTS

15-1 Environmental Laws and Regulations of Japan

15-2 Statement of General Environmental Compliance for Abbott Laboratories, North Chicago Operations from the Director of Abbotts' North Chicago Operations Pharmaceutical Products Division

15-3 Certificate of Environmental Compliance for the Manufacture of Bulk Drug, Leuprolide Acetate, at Hikari Plant of Takeda Chemical Industries, Ltd. From the Director of Environmental Protection Division, Environmental Protection and Public Health Department, Yamaguchi Perfectural Government, Japan

15-4 Certificate of Environmental Compliance from Plant General Manager of Hikari Plant for the Manufacture of Bulk Drug Leuprolide Acetate

15-5 Certificate of Environmental Compliance for the Manufacture of Drug Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg), at Osaka Plant of Takeda Chemical Industries, Ltd. From the Managers of Environmental Pollution Control, Water Quality Control and Industrial Waste Guidance Departments, Osaka City Government, Japan

15-6 Certificate of Environmental Compliance from Plant General Manager of Osaka Plant for the Manufacture of Drug Product, and Vehicle (Lupron Depot® - 3 Month, 11.25 mg)

15-7 Certificate of Environmental Compliance from the Mayor of Fujisawa City for the Manufacture of Drug Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg)

15-8 Certificate of Environmental Compliance from the Director of Shonan Plant, Fujisawa City, Japan

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ATTACHMENT 15-1

Environmental Laws and Regulations of Japan

JAPAN

INTRODUCTION

The Japanese system of environmental law is complicated because, in a great many cases, one single ministry or agency is not the sole administrator of a law. Thus, to ascertain which government bodies or public officials are responsible in a particular instance, it is often necessary to narrow one's enquiry down to the relevant part of that particular law.

Some laws include the names of responsible government agencies. Not listed are other responsible entities such as the Prime Minister's Office and prefectural governors.

Additionally, the Environment Agency, itself, in most cases, is not the final authority when dealing with environmental matters. Actual administrative powers are vested in a number of ministries, agencies, and officials, with the responsible authorities being determined by the content of each particular law.

The Environment Agency

During the rapid economic growth of the 1960s, serious pollution began to manifest itself. A number of laws and regulations were legislated to deal with the situation.

In 1964, the Liaison Council for Environmental Pollution Control was established, and in 1965 the Ministry of Health and Welfare established the Environmental Pollution Inquiry Committee.

Late that same year, the Industrial Pollution Control Special Committee was organized in the Diet. A government agency headed by the Prime Minister, the Central Headquarters for Environmental Pollution Control, was set up in 1970 and, during that same year, in a landmark legislative session known as the "pollution Diet," fourteen pollution-related laws were enacted. These were the events leading to the formation of the Environment Agency.

The Environment Agency was established on July 1, 1971, under the provisions of the Environment Agency Establishment Law (Law No. 88 of May 31, 1971; last amended by Law No. 97 of 1987). Article 3 of this law describes the agency's duties thus:

"The principal duties of the Environment Agency are to comprehensively promote government administration pertaining to environmental preservation in order to control pollution, protect and maintain the natural environment, and provide for environmental preservation in other ways, as well as to contribute to securing a healthful and cultural life for the citizens" (*Kankyo Roppo*, 1988, p. 13).

The Environment Agency, headed by a director-general ranking as a minister of state, can be roughly divided into the Minister's Secretariat, the Planning and Coordination Bureau, the Environmental Health Department, the Nature Conservation Bureau, the Air Quality Bureau, and the Water Quality Bureau, to which have been added other functions, including training institutes and councils. The powers of the director-general include making recommendations to the heads of other government agencies, or requesting information and explanations from them, concerning matters important to environmental preservation.

The general duties of the agency include the formulation and promotion of fundamental environmental policies, coordination of budgeting policies for pollution-control expenditures, the management of appropriations for environmental research and development, and overall coordination of the various government agencies responsible for environmental protection.

Some of the major laws whose enforcement is within the jurisdiction of the agency are the Air Pollution Control Law, the Water Pollution Control Law, the Nature Conservation Law, the Natural Parks Law, the Wildlife Protection and Hunting Law, and the Law Relating to the Regulation of Transfer of Special Birds. The agency also establishes "environmental quality standards." These standards are benchmark values thought to represent desirable maximum levels for certain pollutants, and are usually meant to be attained within a specified length of time. However, the standards themselves, are not legally binding.

General descriptions of the various bureaus follow.

The Minister's Secretariat

The functions of the Minister's Secretariat can be classified and described in the following manner: (1) Accounting; (2) personnel administration; (3) public relations and information concerning environmental administration; (4) surveys of local environmental situations and the gathering/cataloging of pertinent data; (5) promotion of international cooperation; (6) general supervision of the agency's duties; and (7) the general affairs of the Central Council for Environmental Pollution Control.

Through the Secretariat the Environment Agency is directly concerned with the following international conventions:

- Ramsar Convention;
- Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES);
- Convention on the Prevention of Marine Pollution by the Dumping of Waste and other Matter; and
- Protocol of 1978 relating to the International Convention for the Prevention of Pollution from Ships.

Furthermore, bilateral cooperation for the protection of the natural environment and wildlife is conducted with the countries of the United States, the Federal Republic of Germany, France, Canada, Australia, the People's Republic of China, the Republic of Korea, the EC, and ASEAN.

Planning and Coordination Bureau

The bureau is responsible for (1) the formulation and implementation of basic environmental policy; (2) coordinating management, budgets, and research on environmental conservation as assigned to the ministries and agencies associated with environmental protection; (3) expressing opinions concerning national land use and development, and offering guidance on the preparation of regional pollution control programs; (4) the planning, formulation, and promotion of basic policies for environmental impact assessments; (5) preparation of an annual report on environmental quality by the bureau's Office of Planning and Research; and (6) the administration, by the Planning and Coordination Division, of the Environmental Pollution Control Service Corporation, which provides loans for the pollution-control facilities of small- and medium-sized enterprises, as well as the management of the National Institute for Environmental Studies and the Training Institute for Environmental Pollution Control.

With regard to environmental impact assessments, the Planning and Coordination Bureau formulates and promotes the basic policy for assessments, and coordinates related work for assessments among the agencies concerned. The bureau includes an Environmental Impact Assessment Division that handles the scientific and technical questions aris-

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ing with assessments, as well as the examination of assessments and the provision of guidance in their preparation. Environmental assessments will be dealt with in greater detail below.

Environmental Health Department

This department was created to insure full enforcement of the Pollution-Related Health Damage Compensation Law. Through its two divisions, the Planning Division and the Health and Welfare Division, the Environmental Health Department administers the National Institute for Minamata disease, which conducts medical research on Minamata disease, carries on scientific research regarding the diseases caused by pollution, and, through prefectural and local government, provides pollution victims with compensation benefits. Some of the well-known pollution diseases with which the department is concerned are "Itai-itai disease" (cadmium poisoning in Toyama Prefecture), "Minamata disease" (organic mercury poisoning in Kumamoto, Kagoshima, and Niigata prefectures), "Yokkaichi asthma" (a severe respiratory ailment caused by factory air pollution in Yokkaichi City, Mie Prefecture), and chronic arsenic poisoning in the Toroku district of Miyazaki Prefecture.

Additionally, the department, through either of its two divisions: (1) supervises the Pollution-Related Health Damage Compensation Association; (2) performs clerical work for the Pollution-Related Health Damage Compensation Grievance Board; (3) scientifically determines the causes of pollution-related health damage; (4) performs duties related to enforcing the Interim Law Concerning Special Measures for the Promotion of Minamata Disease Certification; and (5) performs work associated with designating the items to be tested for new chemicals pursuant to the Law Concerning the Screening and Regulation of the Manufacture of Chemical Substances.

Nature Conservation Bureau

This bureau concerns itself with a number of areas including: (1) Planning of basic policies for the protection and conservation of the natural environment, (2) surveys of Japan's natural environment by way of the "Green Census" a national survey of the environment, the results of which are employed in the formation of conservation measures, (3) the designation of national parks, quasi-national parks, marine parks, and natural areas requiring conservation, (4) the implementation of measures for the protection, management, and maintenance of natural parks; and (5) the protection and breeding of wildlife. The bureau is responsible for the enforcement of the Natural Parks Law, the Hot Springs Law, the Wildlife Protection and Hunting Law, The Ramsar Convention, and CITES.

There are 27 national parks totaling 2,022,162 hectares in size and 54 quasi-national parks totaling 1,388,774 hectares.

Air Quality Bureau

This bureau is concerned with: (1) The establishment of environmental quality standards, considered desirable in protecting human health and preserving the human living environment, regarding air and noise pollution, vibration, and offensive odors; (2) regulating the amount of soot and dust emitted by factories, and specifying the maximum permissible limits for automobile exhaust emissions (actual regulation of emissions is the province of the prefectural governments); (3) designation of pollution-related areas, regulation of working hours, and specifying permissible automobile noise limits for the purpose of protecting residential environments from the noise and vibration of factories, construction work, and traffic (actual designation is the province of the prefectural and municipal governments); (4) the control of offensive odors from factories (actual control is the province of the prefectural and municipal governments); and (5) the promotion of comprehensive measures to prevent motor vehicle pollution. For this last purpose the bureau established the Automotive Pollution Control Division and the Office of Traffic Pollution Control.

Water Quality Bureau

This bureau is concerned with: (1) The regulation of factory effluents, the establishment of environmental water quality standards for the protection of human health, the preservation of residential environments, and the prevention of water pollution (actual regulation is the province of prefectural governments); (2) the planning and implementation of comprehensive measures for conserving the environment of the Seto Inland Sea, including the maintenance of water quality; (3) the designation of lakes in which water quality has degraded, and the implementation of measures to maintain lake water quality; (4) the specification of waste disposal criteria; (5) the protection of agricultural land from soil pollution, the specification of remedial measures to be implemented in the event of soil contamination, and restrictions on the use of agrochemicals; (6) nationwide surveys of ground subsidence and regulation of groundwater use by industry and construction (actual duties performed by prefectural governments); (7) establishing standards for waste disposal and sewage sludge treatment; and (8) assisting in the planning for river basin sewer construction.

Ground subsidence is the province of the Planning Division, which is responsible for enforcing the Industrial Water Law and the Law Concerning the Regulation of Pumping-Up of Groundwater for Use in Buildings.

The bureau established a Soil and Agricultural Chemicals Division to control soil contamination and the use of agrochemicals. This division determines environmental quality standards for soil contamination, and enforces the Agricultural Land Soil Pollution Prevention Law.

Water pollution is specifically the charge of the bureau's Water Quality Management Division and Water Pollution Control Division, and this includes the duties specified in the Law Concerning Special Measures for Conservation of the Environment of the Seto Inland Sea, for which purpose the Water Pollution Control Division established the Office of Seto Inland Sea Environmental Conservation.

Auxiliary Organs

These eight bodies are as follows: National Institute for Environmental Studies, National Institute for Minamata Disease, Training Institute for Environmental Pollution Control, Pollution-Related Health Damage Compensation Board, Central Council for Environmental Pollution Control, Nature Conservation Council, Seto Inland Sea Environmental Conservation Council, and Special Certification Council for Minamata Disease.

The most important of these with respect to the formulation of environmental policy are:

The Central Council for Environmental Pollution Control, which has a maximum of 90 members appointed by the prime minister for a term of two years. The council deliberates upon important matters relating to environmental measures, and expresses its views, including advice and suggestions, to the prime minister and the director-general of the Environment Agency. It was established on July 1, 1971;

The Nature Conservation Council, which has a maximum of 45 members likewise appointed by the prime minis-

ter for a term of two years. The council investigates and deliberates upon matters of importance to the conservation of the natural environment, and expresses its views to the director-general or other ministers. It was established on April 12, 1973; and

The Seto Inland Sea Environmental Conservation Council, which has a maximum of 34 members appointed by the prime minister for a two-year term. The council investigates and deliberates upon matters of importance to the conservation of the Seto Inland Sea, and expresses its views to the director-general or other ministers. It was established on November 2, 1973.

Corporations

The Environment Agency also supervises two environment-related corporations, the Environmental Pollution Control Service Corporation, which funds corporate relocations and pollution-control facilities at low interest rates, and the Pollution-Related Health Damage Compensation Association, which collects money from polluting industrial facilities and pays this as compensation (through local governments) to pollution patients under the Pollution-Related Health Damage Compensation Law.

Environmental Impact Assessment System

Although efforts at legislation for a national environmental impact assessment (*kankyo eikyo hyoka*) law failed in the Diet, assessments are now normally prepared for large-scale public works projects throughout Japan.

Development of the environmental impact assessment procedures in Japan were initiated with the Cabinet decision of June, 1972 called *Environmental Preservation Countermeasures for Public Works Projects*, and since that time environmental impact assessments have been conducted on the basis of certain laws such as the Public Waters Landfill Law, the administrative guidance of government agencies, and municipal ordinances and guidelines.

Later, on August 28, 1984, a Cabinet decision passed the *Implementation of Environmental Impact Assessments*, thereby establishing the *Guidelines for the Implementation of Environmental Impact Assessments*. In this way the government established a set of uniform procedures to be employed in assessing the impact of large-scale projects with which the national government is associated. The kinds of projects covered include roads, dams, railways, airports, landfills, and land development for urban or industrial use.

The process of preparing an assessment can be roughly divided into four steps and described as follows:

- The developer (i.e., the person or persons undertaking the project), pursuant to the policies established by the concerned minister after conferring with the director-general of the Environment Agency, performs a survey, makes predictions, assesses the impact of the project, and prepares a draft Environmental Impact Statement (EIS). The draft includes the following items: Name and address of developer; purpose and description of project; a summary of the findings obtained in surveys and studies; and an assessment of the project's impact, including proposed pollution control measures.
- The developer publishes the draft, circulating it among concerned parties, and conducts an explanatory meeting. The draft should be made available for public scrutiny for at least one month.
- The developer endeavors to ascertain the opinions of people residing in the affected region and then encourages the mayors of the municipalities in this region to state their opinions to the prefectural governor.
- The developer then rewrites the draft and prepares the final assessment based upon these various opinions.

The resulting document is then employed by the concerned government officials in making decisions affecting the proposed development project. When deemed necessary, these officials may seek the opinion of the Environment Agency's director-general with respect to the assessment.

Environmental impact assessments implemented on the basis of laws such as the *Harbor Law* and the *Public Waters Landfill Law* have included projects such as harbor planning, landfills, locating electric generating plants, and urban planning.

Local governments have also concerned themselves with the need for assessments and, as of 1984, 28 local governments had passed ordinances or instituted guidelines for the preparation of assessments. Four local governments (Hokkaido Prefecture, the Tokyo Metropolitan Government, Kanagawa Prefecture, and Kawasaki City) have ordinances; the other 22 local governments (19 prefectures and 3 cities) have instituted guidelines.

Summaries of Major Laws

General environmental quality is the province of the *Basic Law for Environmental Pollution Control*. The law sets out the responsibilities of developers or those who operate business or industrial enterprises, the national government, local governments, and individual citizens with regard to maintaining the general quality of the environment.

Specifically, the national government is to establish environmental quality standards for air, water, soil contamination, and noise, and enact measures to see that these standards are met. In addition, the government must control land use and the installation of facilities causing pollution; promote the establishment of facilities such as buffer zones, waste disposal plants, and sewage systems to prevent pollution; monitor the state of the environment; conduct surveys to plan measures for pollution control; and disseminate information to the citizens to increase their consciousness concerning the need to prevent environmental pollution. Local governments are to enact the same measures in their local areas.

The law also provides for the formulation of Environmental Pollution Control Programs by the prefectures, the settlement of pollution disputes by the government, and the payment of costs for pollution control.

Chapter IV establishes the Conference on Environmental Pollution Control and the various Councils on Environmental Pollution Control. The latter include prefectural and local councils in addition to the Central Council on Environmental Pollution Control (see "Auxiliary Organs," above).

Water Quality

The purpose of the Water Pollution Control Law is to prevent the pollution of public waters (i.e., rivers, lakes, ports, harbors, irrigation channels, and coastal ocean areas) by wastes discharged from business and industrial facilities, and to effect compensation for damage to human health from water pollution.

Standards for effluents and thermal pollution, specifying maximum permissible amounts for each regulated substance, are established by an ordinance of the Prime Minister's Office. The director-general of the Environment Agen-

cy may also advise prefectures to establish or modify their own standards to be in accordance with this law.

The prime minister is to establish policies to reduce the pollution loads for designated large, nearly closed bodies of water that are subject to considerable amounts of pollution due to heavy population or industrialization. These policies set out objectives, including target dates and amounts by which the pollution loads are to be reduced. The governors of affected prefectures are to establish, on the basis of these policies, their own plans for the attainment of objectives outlined in the government policies.

The law also places restrictions on industrial facilities which discharge certain substances (specified by Cabinet order) into designated bodies of water, and prefectural governors are empowered to order the enactment of remedial measures when a specified facility fails to comply with standards. Governors are also responsible for the monitoring of water quality within their prefectures.

Provisions for compensation have also been included to cover instances in which human health has been damaged by water pollution from industrial facilities.

The Law Concerning Special Measures for the Preservation of Lake Water Quality (Clean Lakes Law), enacted and promulgated on July 27, 1984, provides for the establishment of the basic policy for the preservation of lake water quality by the national government, as well as the drafting of a lake conservation plan for each lake designated under the law, by which actions for lake protection can be implemented, such as the construction of sewage facilities, or the initiation of regulatory actions to reduce pollutants. The law also provides well-defined regulations to control pollution sources and makes it possible to enact special measures for protecting lakes requiring immediate action to meet the Environmental Water Quality Standards of December 15, 1982. Lakes are designated by the prime minister, after which the governor of the affected prefecture prepares a plan for the preservation of lake water quality.

The Law Concerning Special Measures for Conservation of the Inland Sea promotes the conservation of the Seto Inland Sea by establishing a basic plan for conservation of the environment of the Seto Inland Sea by the national government, and "prefectural plans" to be established by the adjoining prefectures for the parts of the Inland Sea off their shores. Furthermore, special conservation measures place restrictions on the establishment of industrial facilities and their effluents; permission must be obtained from prefectural governors before building facilities of a certain type and scale.

Other sections of the law place restrictions on substances such as phosphorus to prevent eutrophication, or provide for the designation of "natural seashores" by the prefectures to protect sand beaches, reefs, or public swimming areas.

The law also requires the national government to organize a system to deal with oil spills in the Inland Sea, to ascertain the mechanism by which algae blooms occur (specifically, the "red tide") and to provide relief for fishermen who suffer losses because of oil spills or the red tide.

Marine pollution and accidents at sea are to be prevented by the *Law Relating to the Prevention of Marine Pollution and Maritime Disaster*. The law prohibits, except in certain cases, the discharge of oils or oily mixtures, noxious liquid substances (other liquids designated by Cabinet order), or wastes from vessels at sea, and stipulates the kinds of equipment and facilities that seagoing vessels are to have, as well as their methods of operation and record-keeping. The minister of transport is responsible for carrying out periodic inspections of the marine pollution prevention facilities (bilge discharge prevention facilities, water ballast discharge prevention facilities, and a segregated ballast tank), and may order modifications or repairs to such when it is found that they do not conform with standards.

The law also prohibits the discharge of oil and wastes into the sea from offshore facilities and aircraft, and provides for controls on the incineration of oil, noxious liquid substances, or wastes on board ship or at offshore facilities. In addition, the minister of transport is given the responsibility for issuing permits to operate waste oil disposal businesses.

The law outlines procedures for the prevention of marine pollution and maritime disaster, as well as for dealing with oil spills, fires, collisions, and other accidents and disasters at sea.

A Maritime Pollution Prevention Center is also incorporated under the law to prevent or deal with maritime disasters, and to protect human life and property.

The *Industrial Water Law* provides for measures to assure a water supply for industrial development, to promote the conservation of groundwater resources, and prevent ground subsidence.

The law controls the use of groundwater by industries within areas designated by Cabinet order. Such areas are designated when, due to the excess use of groundwater, the level of the water table has become extremely low, ground subsidence has occurred, or when salt water or foul water has invaded the groundwater supply. Permission for the use of wells is granted by prefectural governors.

Another law whose purpose is to prevent ground subsidence is the *Law Concerning the Regulation of Pumping-Up of Underground Water for Use in Buildings*. This law controls the use of groundwater for industrial use pursuant to the Industrial Water Law, above, and for other kinds of facilities designated by Cabinet order, such as air conditioning and flush toilets.

Similar to the foregoing law, areas in which groundwater use is to be regulated are designated by Cabinet order. Persons wishing to draw and use underground water in designated areas must receive permission from prefectural governors, city mayors, or other public officials.

Air Quality

The *Air Pollution Control Law* sets maximum permissible limits for motor vehicle exhausts and other emissions, and regulates industrial soot and smoke emissions. Regulated emissions include sulfur oxides, cadmium, chlorine, hydrogen fluoride, lead, particulate matter, carbon monoxide, and hydrocarbons produced by combustion, synthesis, mechanical processes, or resolution. However, the law is not applicable to air pollution caused by radioactive materials.

Emission standards for facilities emitting soot and smoke are set by the Prime Minister's Office, while the maximum permissible limits on motor vehicle emissions are established by the director-general of the Environment Agency, who may also recommend emission standards for industrial facilities to prefectural governors. Prefectural governors are responsible for measuring the concentration of motor vehicle exhaust gases in areas with heavy traffic, for periodically monitoring the general level of air pollution, and for publicly announcing the extent of air pollution in their prefectures. Governors are also empowered to enact measures when necessary in order to reduce air pollution when human health is endangered.

Businesses and industries are required to provide compensation for damage to human health as a result of their emissions, and the law also provides for fines or imprisonment for violators.

Unpleasant odors produced by industrial or business facilities are subject to regulation by the *Offensive Odor*

Controlled Substances. Substances covered by the law are the eight substances listed in the Cabinet Order, including ammonia, methyl mercaptan, hydrogen sulfide, and styrene.

Prefectural governors are required, after consultation with the mayors of local governments, to designate areas in which odors are to be regulated, as well as the regulation standards. Maximum concentrations in the air are set for substances produced at ground level, emitted from smoke stacks, and discharged in aqueous effluents. Governors are also charged with measuring concentrations of the stipulated substances within designated areas.

In the event of an accident in which the stipulated substances are discharged into the environment to the extent that regulation standards are exceeded, businesses are required to take immediate remedial action.

The law also prohibits burning in the open air large quantities of substances such as rubber, hides, and synthetic resins in densely populated areas.

Pollution Control

Specific punishments for pollution related offences, including fines and imprisonment, are stipulated by the *Law for the Punishment of Crimes Relating to the Environmental Pollution which Adversely Affects the Health of Persons.* Both representatives or employees of a business or corporation, and the business entity itself, may be subject to punishment when, either with intent or through negligence, it is found to be adversely affecting human health, endangering human life, or causing death through the discharge of harmful substances.

Business and industries are required by the *Pollution Control Public Works Cost Allocation Law* to install facilities for the prevention of pollution, or to undertake projects to repair pollution-caused damage, such as dredging, sludge removal, or topsoil replacement. The law specifies the procedures by which is determined the percentage of the costs that a business or industry shall pay, and the methods for their payment.

Compensation for Pollution Victims

The Pollution-Related Health Damage Compensation Law, a major piece of legislation for redressing the damage of pollution to human health, provides for the designation, by Cabinet order, of regional and diseases, and the payment of seven types of compensation benefits to pollution victims or their survivors. The benefits are: (1) Medical care benefits and expenses, (2) compensation for handicaps, (3) compensation for survivors, (4) lump-sum compensation payments for survivors, (5) child compensation allowances, (6) medical care allowances, and (7) funeral expenses. Prefectural governors follow detailed criteria in certifying pollution victims, who then become eligible for benefits. According to the law, each prefecture and city located within a designated region must establish a Pollution-Related Health Damage Compensation Council, consisting of a maximum of 15 persons, which assists the implementation of the law in each locality. The Pollution-Related Health Damage Compensation Association (established by Chapter 5 of the law, see the section "Corporations" under the Environment Agency, above) is to collect levies from industrial facilities producing soot and smoke, and these funds are used to pay benefits. Eighty percent of all benefits awarded under this system are obtained from these levies, and the other 20 percent are derived from automobile tonnage tax. In addition, the law provides for the establishment of a Pollution-Related Health Damage Compensation Coverage Board (see "Environmental Health Department" under the Environment Agency, above) to handle complaints from persons who are dissatisfied with the action taken on their behalf.

A major amendment was effected on March 1, 1988 when the regional designations for air pollution-related health damage established under the law were completely canceled, the reason being that air pollution has decreased substantially, thereby no longer constituting the principal cause of disorders such as asthma. In addition, facilities in all parts of Japan that emit sulfur oxides had been subject to levies, even if they were outside the designated regions. In view of the increasing number of certified patients, and the concomitant increasing total amount of benefits, as well as the fact that nearly 70 percent of the costs were being borne by undesignated regions, the Central Council on Environmental Pollution Control recommended, among other measures, that (1) all designations be canceled, (2) compensation benefits continue to be paid to certified patients, and (3) stronger measures be implemented to prevent air pollution. The amendment provides for the continuing payment of benefits to patients already certified, with the amount of levies on SO_x-emitting facilities being determined on the basis of their emissions over a certain amount of time prior to the cancellation of regional designations.

A total of 41 regions in 10 prefectures (19 of them Tokyo wards) had been designated, and the number of certified patients throughout Japan had grown from 19,200 at the beginning of the program to 107,523 as of January, 1988. Paid benefits for FY 1986 totaled approximately ¥100 billion (US$800 million).

Food and Chemicals

The purpose of the *Law Concerning the Screening and Regulation of the Manufacture of Chemical Substances* is to prevent environmental contamination by chemical substances which decompose with difficulty, and which may present a danger to human health. To this end, new chemical substances are screened prior to manufacture or importation to determine their properties, and to place any necessary controls on their manufacture, importation, or use. Chemical substances subject to controls under this law exclude radioactive substances and those controlled by other laws, such as poisons, stimulants, and narcotics.

The purpose of the *Food Sanitation Law* is to prevent harm arising from food sanitation problems. It requires that all foods sold are sanitary, including all implements and containers used for their collection, manufacture, processing, use, preparation, storage, transport, display, and transferral, and in general prohibits the handling or sale of contaminated, unripe, unclean, or decayed foods, as well as meat and other parts and products from wild or domestic animals that have died of illness. The law also makes provisions for prohibiting the sale of newly developed foods and food additives which have not been approved. In addition, the Minister of Health and Welfare is empowered to establish criteria and standards for the manufacture, processing, use, preparation, and preservation of foods and food additives, as well as their containers and packaging.

Agriculture and Agricultural Chemicals

The purpose of the *Agricultural Land Soil Pollution Prevention Law* is to prevent harm to crops and human health by preventing or removing harmful substances which contaminate agricultural land. Prefectural governors are empowered to designate certain areas of agricultural land

the agricultural produce of which has been found to contain certain levels of harmful substances (cadmium, copper, arsenic, and their compounds), as "agricultural land soil pollution policy areas." Governors then formulate plans for these areas which provide for appropriate land use, construction of, or modifications in, drainage or irrigation facilities in order to prevention soil contamination, and projects designed for the purpose of eliminating soil contamination.

The Agricultural Chemicals Regulation Law establishes a registration system, and regulates the sale and use of agrochemicals (including natural enemies used for pest control).

Official standards for the amounts of active ingredients and harmful ingredients are set by the Minister of Agriculture, Forestry, and Fisheries. The Minister also grants registrations to agrochemical manufacturers and importers (including foreign manufacturers who export to Japan), who may not sell manufactured, imported, or processed chemicals in Japan without registration. Proper labeling is also required for sale.

The government may also designate agrochemicals as those which tend to show residual properties in soil or crops, or which contaminate water supplies. The government may institute certain controls over agrochemicals thus designated.

This law does not apply to any agrochemicals which are manufactured, processed, or sold for the purpose of export.

Waste Disposal

The disposal of both domestic and industrial wastes is the province of the *Waste Disposal and Refuse Collection Law*.

The law requires businesses and industry to correctly dispose of the industrial wastes generated in their operations, as well as to recycle their wastes to the greatest extent possible in order to reduce the total amount. They must also endeavor to see that the subsequent disposal of the discarded products or containers used in manufacturing, processing and sales shall not present them with undue difficulties. Municipalities may dispose of industrial wastes when those waters are of a kind which may be disposed of with domestic wastes. Prefectural governors are responsible for planning industrial waste disposal.

The law specifies that municipal governments are responsible for collecting and disposing of domestic wastes in their areas, and also outlines the procedures for establishing and operating domestic waste disposal plants, as well as private waste disposal tank cleaning businesses.

Noise and Vibration

The Noise Regulation Law sets maximum permissible levels for motor vehicle noise, and regulates the noise generated by industrial and construction sites.

Areas subject to industrial noise level controls are designated by prefectural governors after consulting with city, town, and village mayors in the areas concerned. Such areas are those with, for example, schools, hospitals, or densely populated residential districts. Governors then establish regulatory standards, with respect to certain hours and zones, for the businesses and industries (determined by Cabinet order) located in these areas.

In the event that levels of noise in a designated area are found to be unsatisfactory with respect to the regulatory standards, prefectural governors are empowered to recommend improvements to ameliorate noise, and, if these recommendations are not followed within a stipulated period of time, issue an executive order requiring the implementation of such improvements.

Maximum permissible levels for motor vehicle noise are set by the director-general of the Environment Agency, and these levels must be observed by the minister of transport when regulating motor vehicle noise under the Road Transportation Vehicles Law.

The Vibration Regulation Law controls the vibration caused by industrial and construction sites, and provides a channel for requests by prefectural governors regarding road improvements for the control of road traffic vibration.

As with the Noise Regulation Law, prefectural governors designate areas and then establish regulatory standards for vibration from industrial facilities and construction sites.

If levels of vibration in a designated area are found to be unsatisfactory with respect to the regulatory standards, prefectural governors are empowered to recommend improvements to ameliorate vibration, and, if these recommendations are not followed, issue an order requiring the implementation of such improvements.

If monitoring results indicate that road traffic vibration has exceeded the limits set by an ordinance of the Prime Minister's Office, prefectural governors are empowered to ask the road administrator or the Prefectural Public safety Commission to take appropriate remedial action.

Nature Protection

The Nature Conservation Law states the obligations of the national government, local governments, business and industry, and the citizens in conserving the natural environment and establishes a Nature Conservation Council in the Environment Agency. The council discusses and conducts studies on matters related to the provisions of this law and others concerned with wildlife protection (see "Auxiliary Organs" in the section on the Environment Agency).

The law provides for the designation of wilderness areas by the director-general of the Environmental Agency, and conservation plans for these areas are established upon consultations with prefectural governors and the Nature Conservation Council. All development, mineral exploitation, capturing or collection of wildlife, use of powered vehicles, and other such activities are prohibited.

The director-general may also designate nature conservation areas in parts of the country that are in need of preservation due to their special or unique qualities. A conservation plan for each such area is formulated by the Director-General, and certain development activities are prohibited within the areas.

In addition to these areas, the director-general is empowered to create "wildlife protection districts" and "special marine areas" for reasons of conservation. These districts and areas too are subject to certain restrictions on development and other activities.

The purpose of the *Natural Parks Law* is the protection of places of scenic beauty, and the promotion of their use, thereby contributing to the health, recreation, and cultural education of the citizens. Natural parks include national parks, quasi-national parks, and prefectural national parks. National parks and quasi-national parks are designated by the the director-general of the Environment Agency after consultations as specified by this law. Prefectural national parks are designated by the respective prefectural governments. Marine park areas may also be designated by the director-general. The law provides for the protection, maintenance, and utilization of natural parks, as well as prescribing certain activities within park boundaries.

The purposes of the *Wildlife Protection and Hunting Law* are to improve the living environment of the citizens and to provide agriculture, forestry, and fisheries by implementing projects for the protection of wildlife, providing for appropriate hunting, and controlling "harmful wildlife."

Prefectural governors are to establish plans for wildlife protection projects, in accordance with standards set by the director-general of the Environment Agency, which provide for propagation, hunting, habitat surveys, and the control of harmful wildlife. The law also makes provisions for the various classes of hunting licenses and the requirements for their acquisition, as well as the establishment and management of hunting areas.

Regulatory measures for the protection of endangered species of birds are provided for by the *Law Relating to the Regulation of Transfer of Special Birds*. "Special birds" and their eggs, i.e., birds in danger of extinction in either Japan or other countries, and designated as such by the Prime Minister's Office, may not be imported, exported, or otherwise transferred unless permission has been granted by the director-general of the Environment Agency or, in the case of imports, unless a certificate granting permission has been obtained from the government of the exporting country.

The *Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora* was created as a domestic law to work in conjunction with the Convention on International Trade in Endangered Species of Flora and Fauna (CITES), and prohibits the purchase, sale, or other transfer of rare species of flora and fauna, including their eggs, seeds, and derivatives, as defined by Cabinet order. The law provides for several exceptions to this provision, as when, for example, the director-general of the Environment Agency allows such transfer for scientific research or breeding.

Public display of rare species of flora and fauna is prohibited, and specimens that have been commercially bred or are covered by a Cabinet order must be officially registered. Registration certificates are issued by the director-general of the Environment Agency. When a registered specimen is purchased, sold, or otherwise transferred, the registration certificate must accompany the specimen.

The director-general is further empowered to direct inspections of registered specimens and the conditions under which they are kept, and to offer advice pertaining to the improvement of such conditions.

Land Use and Development

The *Public Waters Landfill Law* makes provisions for obtaining a license from the prefectural governor in order to landfill or otherwise reclaim a part of a river, the sea, or a lake (i.e., "public waters," or those in the possession of the national government), for compensation when the landfill operation prevents effective use of the concerned area of water, and for the procedures to be observed in the operation.

The Harbor Law stipulates that creation of a harbor should not degrade the surrounding environment, and that the residential environment of people living in the vicinity should be preserved, or degradation kept to a minimum. The law provides that the developer may be required to pay part of the expenses incurred in this environmental preservation. See the section on the Environmental Impact Assessment System.

DIRECTORY OF AGENCIES

Administering Agencies

Many Japanese government ministries, agencies, and offices are in some way, directly or indirectly, involved in environmental administration, but the major government bodies are as follows:

Environment Agency (Kankyo-cho)

No. 5 Joint Government Building (19th to 22nd Floors)
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100
Telephone: (03) 581-3351

Ministry of International Trade and Industry (Tsushosangyo-sho or Tsusan-sho)

2-1 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 501-1511
Industrial Location and Environmental Protection Bureau, Industrial Location Guidance Division, Industrial Water Division, Safety Division, Chemical Products Safety Division, Machinery and Information Industries Bureau, Consumer Goods Industries Bureau.

Ministry of Health and Welfare (Kosei-sho)

2-2 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 503-1711
Food Sanitation Division, Environmental Health Bureau, Veterinary Sanitation Division, Food Chemistry Division, Water Supply and Environmental Sanitation Department, Waste Management Division, Pharmaceuticals and Chemicals Safety Division, Pharmaceuticals Affairs Bureau.

Ministry of Agriculture, Forestry, and Fisheries (Norinsuisan-sho)

2-1 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 502-8111
Regional Planning Division, Planning Department, Agricultural Structure Improvement Bureau, Crop Production Division, Agricultural Production Bureau, Plant Protection Division, Processing Industry Division, Food and Marketing Bureau.

Ministry of Construction (Kensetsu-sho)

1-3 Kasumigaseki 2-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 580-4311
Building Land Development Division, Economic Affairs Bureau, City Planning Division, City Bureau, Parks and Greens Division, Sewerage and Sewage Purification Division, River-Basin Sewerage Division, Public Sewerage Division, Water Administration Division, River Bureau (this bureau administers landfill operations), Development Division, Road Administration Division, Road Bureau.

National Land Agency (Kokudo-cho)

2-2 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 503-2311
Land Use Planning and Control Division, Land Bureau, Water Resources Planning Division, Water Resources Department, Regional Development Bureau, Urban Area Development Division.

Prime Minister's Office (Sorifu)

1-6-1 Nagata-cho
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-2361

National Public Safety Commission (National Police Agency) (Keisatsu-cho)

1-2 Kasumigaseki 2-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-0141
Pollution Control Division, Safety Department, Criminal Investigation Bureau (this agency is responsible for the enforcement of regulations according to the Basic Law for Environmental Pollution Control).

Environmental Disputes Coordination Commission (Kogai-to Chosei Iinkai)

1-6-1 Nagata-cho
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-2361
General Affairs Division, Investigations.

Forestry Agency (Rinya-cho)

2-1 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 502-8111
Planning Division, Private Forest Department, Silviculture Division, Forest Road Division, Forest Protection Division.

Fisheries Agency (Suisan-cho)

2-1 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 502-8111
Fishing Port Planning Division, Fishing Port Department, Fishing Ground
Preservation Division.

Science and Technology Agency (Kagakugijutsu-cho)

2-2-1 Kasumigaseki
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-5271
Responsible for radioactive wastes (the Environment Agency is not connected in any way with radioactive waste management).

JAPAN
LIST OF SELECTED LAWS AND REGULATIONS

Major Laws, Orders, Enforcement Rules

General:

Basic Law for Environmental Pollution Control (Law No. 132 of 1967; last amended by Law No. 78 of 1972).

Law for the Punishment of Crimes Relating to the Environmental Pollution which Adversely Affects the Health of Persons (Law No. 142 of 1970).

Air Pollution and Odors:

Air Pollution Control Law (Law No. 97 of 1968; last amended by Law No. 65 of 1974; Environment Agency, National Police Agency, Ministry of Transport, and Ministry of International Trade and Industry).

Cabinet Order for Implementation of the Air Pollution Control Law (Law No. 229 of 1968; last amended by Cabinet Order No. 162 of 1983).

Enforcement Regulation of the Air Pollution Control Law (Ministry of Health and Welfare and Ministry of International Trade and Industry Ordinance No. 1 of June 22, 1971; last amended by Prime Minister's Office Ordinance No. 53 of 1987).

Offensive Odor Control Law (Law No. 91 of 1971; Environment Agency, Ministry of Agriculture, Forestry, and Fisheries).

Cabinet Order and Ordinance of the Prime Minister's Office for the Offensive Odor Control Law (Cabinet Order No. 207 of 1972; amended by Ordinance of Prime Minister's Office No. 49 of 1976).

Environmental Quality Standards Regarding Air Pollution (Environment Agency Notification No. 25, May 8, 1973; amended by Notification No. 47 of 1981).

Environmental Quality Standard for Nitrogen Dioxide (Environment Agency Notification No. 38, 1978).

Noise and Vibration:

Regulatory Standards for Noise Emitted from Specified Factories (Notification No. 1 of November 27, 1968, from the Ministry of Health and Welfare, Ministry of Agriculture, Forestry and Fisheries, Ministry of International Trade and Industry, and Ministry of Transport; amended by Environment Agency Notification No. 11 of 1986).

Standards for Noise from Special Construction Works (Ministry of Health and Welfare, and Ministry of Construction Notification No. 1 of November 27, 1968; amended by Environment Agency Notification No. 12 of 1987).

Environmental Quality Standards for Noise (Cabinet Decision of May 25, 1981).

Environmental Quality Standards for Shinkansen Superexpress Railway Noise (Environment Agency Notification No. 46 of July 29, 1975).

Environmental Quality Standards for Aircraft Noise (Environment Agency Notification No. 154 of December 27, 1973).

Noise Regulation Law (Law No. 98 of 1968; last amended by Law No. 88 of 1971; Environment Agency, National Police Agency, Ministry of Transport).

Cabinet Order for Implementation of the Noise Regulation Law (Cabinet Order No. 324 of 1968; last amended by Cabinet Order No. 22 of 1986).

Vibration Regulation Law (Law No. 64 of 1976; Environment Agency, National Police Agency).

Cabinet Order for the Implementation of the Vibration Regulation Law (Cabinet Order No. 280 of 1976; amended by Cabinet Order No. 22 of 1986).

Regulatory Standards for Vibration Emitted from Specified Factories (Environment Agency Notification No. 90 of November 10, 1976; amended by Environment Agency Notification No. 13 of 1986).

Standards for Vibration Emitted from Specified Construction Works (Ministry of Health and Welfare, and Ministry of Construction Notification No. 1 of November 27, 1968; amended by Environment Agency Notification No. 1 of 1986).

Water Pollution:

Water Pollution Control Law (Law No. 138 of 1970; last amended by Law No. 90 of 1985; Environment Agency, Ministry of Transport).

Cabinet Order for Implementation of the Water Pollution Control Law (Cabinet Order No. 188 of 1971; last amended by Cabinet Order No. 89 of 1987).

Water Pollution Control Law Enforcement Regulations (Order No. 2 of June 19, 1971 of the Prime Minister's Office, and the Ministry of International Trade and Industry; last amended by Prime Minister's Office Order No. 67 of 1986).

Law Concerning Special Measures for the Preservation of Lake Water Quality (Law No. 61 of 1984; amended by Law No. 69 of 1984; commonly known as the "Clean Lakes Law"; Environment Agency, Ministry of Transport).

Enforcement Order of the Law Concerning Special Measures for the Preservation of Lake Water Quality (Cabinet Order No. 37 of March 28, 1985; last amended by Cabinet Order No. 314 of 1987).

Enactment Regulations of the Law Concerning Special Measures for the Preservation of Lake Water Quality (Prime Minister's Office Order No. 7 of March 29, 1985; amended by Prime Minister's Office Order No. 44 of 1985).

Law Concerning Special Measures for Conservation of the Environment of the Seto Inland Sea (Law No. 110 of October 2, 1973; last amended by Law No. 63 of June 13, 1978, Environment Agency, Ministry of Transport).

Soil Contamination, Agricultural Chemicals:

Agricultural Land Soil Pollution Prevention Law (Law No. 139 of 1970; last amended by Law No. 87 of 1978; Environment Agency, Ministry of Agriculture, Forestry, and Fisheries).

Cabinet Order for Implementation of the Agricultural Land Soil Pollution Prevention Law (Cabinet Order No. 284 of 1971; last amended by Cabinet Order No. 183 of 1975)

Agricultural Chemicals Regulation Law (Law No. 82 of 1948; last amended by Law No. 23 of 1984; Environment Agency, Ministry of Health and Welfare, Ministry of Agriculture, Forestry, and Fisheries, Ministry of International Trade and Industry).

Cabinet Order for Implementation of the Agricultural Chemicals Regulation Law (Cabinet Order No. 56 of 1971; last amended by Cabinet Order No. 60 of 1987).

Ground Subsidence:

Law Concerning the Regulation of Pumping-Up of Underground Water for Use in Buildings (Law No. 100

of 1962; last amended by Law No. 88 of 1971; Environment Agency, Ministry of International Trade and Industry).

Cabinet Order for the Implementation of the Law Concerning the Regulation of Pumping-Up of Underground Water for Use in Buildings (Cabinet Order No. 325 of 1962; last amended by Cabinet Order No. 302 of 1974).

Industrial Water Law (Law No. 146 of 1956; last amended by Law No. 88 of 1972; Environment Agency, Ministry of International Trade and Industry).

Cabinet Order for the Implementation of the Industrial Water Law (Cabinet Order No. 142 of 1957; last amended by Cabinet Order No. 54 of 1987).

Wastes and Marine Pollution

Waste Disposal and Refuse Collection Law (Law No. 137 of 1970; last amended by Law No. 87 of 1987; Environment Agency, Ministry of Health and Welfare).

Cabinet Order for Implementation of the Waste Disposal and Refuse Collection Law (Cabinet Order No. 300 of September 23, 1971; last amended by Cabinet Order No. 292 of 1987).

Law Relating to the Prevention of Marine Pollution and Maritime Disaster (Law No. 136 of 1970; last amended by Law No. 40 of 1987; Environment Agency, Ministry of Transport, Maritime Safety Agency).

Cabinet Order for Implementation of the Law Relating to the Prevention of Marine Pollution and Maritime Disaster (Cabinet Order No. 281 of June 22, 1971; last amended by Cabinet Order No. 115 of 1987).

Chemical Substances

Law Concerning the Screening and Regulation of the Manufacture of Chemical Substances (Law No. 117 of October 16, 1973; last amended by Law No. 44 of 1986, Environment Agency, Ministry of Health and Welfare, Ministry of Agriculture, Forestry, and Fisheries, Ministry of International Trade and Industry).

Cabinet Order for the Implementation of the Law Concerning the Screening and Regulation of the Manufacture of Chemical Substances (Cabinet Order No. 202 of June 7, 1973; last amended by Cabinet Order No. 49 of 1987).

Food Sanitation Law (Law No. 233 of December 24, 1947; last amended by Law No. 108 of 1972; Ministry of Health and Welfare).

Compensation, Settlement of Disputes

Pollution-Related Health Damage Compensation Law (Law No. 111 of October 5, 1973; last amended by Cabinet Order No. 368 of November 6, 1987; Environment Agency, Ministry of International Trade and Industry).

Enforcement Order of the Pollution-Related Health Damage Compensation Law (Cabinet Order No. 295 of August 20, 1974; last amended by Cabinet Order No. 368 of 1987).

Pollution Disputes Settlement Law (Law No. 108 of June 1, 1970; last amended by Law No. 90 of 1985; Environmental Disputes Coordination Commission).

Costs and Assistance

Pollution Control Public Works Cost Allocation Law (Law No. 133 of December 25, 1970; amended by Law No. 43 of 1987; Environment Agency, Ministry of Finance, Ministry of Health and Welfare, Ministry of Construction, Ministry of Home Affairs).

Cabinet Order for Implementation of the Pollution Control Public Works Cost Allocation Law (Cabinet Order No. 146 of May 8, 1971; last amended by Cabinet Order No. 214 of 1986).

Nature Conservation

Nature Conservation Law (Law No. 85 of 1972; last amended by Law No. 58 of 1987; Environment Agency).

Natural Parks Law (Law No. 161 of 1957; last amended by Law No. 87 of 1972; Environment Agency).

Wildlife Protection and Hunting Law (Law No. 32 of April 4, 1918; last amended by Law No. 83 of 1983; Environment Agency).

Cabinet Order for the Implementation of the Wildlife Protection and Hunting Law (Cabinet Order No. 254 of August 31, 1953; last amended by Cabinet Order No. 106 of April 14, 1979).

Enforcement Regulation for the Wildlife Protection and Hunting Law (Ordinance of the Ministry of Agriculture and Forestry No. 108 of September 30, 1950; last amended by Ordinance of the Prime Minister's Office No. 45 of 1983).

Law Relating to the Regulation of Transfer of Special Birds (Law No. 45 of 1972; amended by Law No. 85 of 1972; Environment Agency).

Order for the Implementation of the Law Relating to the Regulation of Transfer of Special Birds (Cabinet Order No. 405).

Implementation Ordinance for Law Relating to the Regulation of Transfer of Special Birds (Ordinance of Prime Minister's Office No. 71 of November 27, 1972; last amended by Ordinance of the Prime Minister's Office No. 42 of 1985).

Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora (Law No. 58 of June 2, 1987; Environment Agency).

Implementation Ordinance for the Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora (Cabinet Order No. 375 of November 6, 1987).

Enforcement Regulations for the Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora (Ordinance of the Prime Minister's Office No. 55 of December 1, 1987).

Basic Policy on Conservation of the Natural Environment (Prime Minister's Office Notification No. 30 of November 6, 1973).

Land Use and Urban Planning

Urban Planning Law (Law No. 100 of June 15, 1968; last amended by Law No. 66 of 1987; National Land Agency, Ministry of Transport, Ministry of Construction).

Public Waters Landfill Law (Law No. 57 of 1921; last amended by Law No. 5 of 1979).

Harbor Law (Law No. 218 of May 31, 1950; amended by Law No. 87 of 1987)

ATTACHMENT 15-2

Statement of General Environmental Compliance for Abbott Laboratories, North Chicago Operations from the Director of Abbotts' North Chicago Operations, Pharmaceutical Products Division

ABBOTT

Chemical and Agricultural Products Division

Abbott Laboratories
1401 Sheridan Road
North Chicago, Illinois 60064-4000

ABBOTT LABORATORIES
CHEMICAL AND AGRICULTURAL PRODUCTS DIVISION
NORTH CHICAGO, ILLINOIS

GENERAL ENVIRONMENTAL COMPLIANCE STATEMENT

Abbott Laboratories states that it is in material compliance with, or on an internal or enforceable schedule to be in compliance with, all applicable emission requirements set forth in permits, consent decrees and administrative orders relating to the production of Leuprolide Acetate bulk drug at its facilities in North Chicago, Illinois, as well as applicable emission requirements set forth in federal, state and local statutes and regulations relating to such production.

Daniel J. Wozniak
Senior Environmental Coordinator
Chemical and Agricultural Products Division

20 Jan 97
dated

ABBOTT LABORATORIES

PHARMACEUTICAL PRODUCTS DIVISION
NORTH CHICAGO OPERATIONS
1401 SHERIDAN ROAD
NORTH CHICAGO, ILLINOIS 60064-4000

PHARMACEUTICAL PRODUCTS DIVISION

GENERAL ENVIRONMENTAL COMPLIANCE STATEMENT

ABBOTT LABORATORIES states that it is in material compliance with, or on an enforceable schedule to be in compliance with, applicable emission requirements set forth in permits, consent decrees and administrative orders relating to the production of LUPRON DEPOT, at its facilities in North Chicago, Illinois, as well as applicable emission requirements set forth in federal, state and local statutes and regulations, relating to the production of LUPRON DEPOT.

Michael J. Warmuth — 1/21/97

MICHAEL J. WARMUTH, Director, North Chicago Operations
Pharmaceutical Products Division

Date

ATTACHMENT 15-3

Certificate of Environmental Compliance for the Manufacture of Bulk Drug, Leuprolide Acetate, at Hikari Plant of Takeda Chemical Industries, Ltd. From the Director of Environmental Protection Division, Environmental Protection and Public Health Department, Yamaguchi Perfectural Government, Japan

Environmental Assessment

To whom it may concern :

This is to affirm that the Hikari plant of TAKEDA Chemical Industries, Ltd. is manufacturing Leuprolide Acetate bulk in Compliance with all applicable Yamaguchi Prefectural and Japanese national environmental regulations.

Date 28. 7. 1995

Signed by Setsuo Onaka

Setsuo Onaka

Director, Environmental Protection Division
Environmental Protection and Public Health Department
Yamaguchi Prefectural Government

山口県
環境保健部
環境保全課長
尾中 節

ATTACHMENT 15-4

Certificate of Environmental Compliance from Plant General Manager of Hikari Plant for the Manufacture of Bulk Drug Leuprolide Acetate

Environmental Assessment

To whom it may concern :

This is to affirm that the Hikari plant of TAKEDA Chemical Industries, Ltd. is manufacturing Leuprolide Acetate bulk in Compliance with all applicable Yamaguchi Prefectural and Japanese national environmental regulations.

Date 28. 7. 1995

Signed by Setsuo Onaka

Setsuo Onaka

Director, Environmental Protection Division
Environmental Protection and Public Health Department
Yamaguchi Prefectural Government

山口県
環境保健部
環境保全課長
尾中 節

Environmental Assessment

To whom it may concern :

This is to confirm that the Hikari plant of TAKEDA Chemical Industries, Ltd. is manufacturing Leuprolide Acetate bulk in Compliance with all applicable Yamaguchi Prefectural and Japanese national environmental regulations.

Date 28 July 1995

Signed by Tetsuji Shikama

Tetsuji Shikama

General Manager
Hikari plant
TAKEDA Chemical Industries, Ltd.

4720, Mitsui, Hikari-city, Yamaguchi,
Prefecture, Japan

ATTACHMENT 15-5

Certificate Environmental Compliance for the Manufacture of Drug Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg), at Osaka Plant of Takeda Chemical Industries, Ltd. From the Managers of Environmental Pollution Control, Water Quality Control and Industrial Waste Guidance Departments, Osaka City Government, Japan

Environmental Assessment

To whom it may concern :

This is to affirm that facilities for Lupron Depot (drug product and diluent) manufacturing in Osaka Plant of TAKEDA Chemical Industries, Ltd. (17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka, Japan) comply with all laws and regulations on the on air pollution control which were established by local Osaka Prefecture and Japanese national government.

Date MAY. 11. 1995

Signed by Iwao Okayama

Iwao Okayama

Manager

Environmental Pollution Control Dept.

Environment Division

Environment and Public Health Bureau

Osaka City Government

Environmental Assessment

To whom it may concern :

This is to affirm that waste water control facilities for Lupron Depot (drug product and diluent) manufacturing in Osaka Plant of TAKEDA Chemical Industries, Ltd. (17-85, Jusohonmachi-2-chome, Yodogawa-ku, Osaka, Japan) comply with all laws and regulations on the water pollution control which were established by local Osaka City and Japanese national government.

Date 1995. 5. 16.

Signed by Masakazu Fukuchi

Masakazu Fukuchi

Manager

Water Quality Control Department

Management Division

Sewage Works Bureau

Osaka City Government

Environmental Assessment

To whom it may concern :

This is to affirm that disposal methods of industrial wastes generated in the Lupron Depot (drug product and diluent) manufacturing in Osaka Plant of TAKEDA Chemical Industries, Ltd. (17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka, Japan) comply with all laws and regulations on the indutrial wastes disposal which were established by local Osaka City and Japanese national government.

Date 1995. 5. 16

Signed by Kunio Takemura

Kunio Takemura

Manager

Industrial Waste Guidance Department

Service Division

Environmental Management Bureau

Osaka City Government

ATTACHMENT 15-6

Certificate of Environmental Compliance from Plant General Manager of Osaka Plant for the Manufacture of Drug Product, and Vehicle (Lupron Depot® - 3 Month, 11.25 mg)

CONFIDENTIAL DOCUMENT
TAKEDA PROPERTY

PRODUCTION DIVISION
PHARMACEUTICAL GROUP
TAKEDA CHEMICAL INDUSTRIES, LTD.

Environmental Assessment

To whom it may concern :

This is to confirm that Manufacturing of Lupron Depot (drug product and diluent) complies with all applicable local Osaka Prefecture and Japanese national environmental regulations.

Date May 8, 1995

Signed by Toshiyuki Okuno

Toshiyuki Okuno

General Manager

Osaka plant

TAKADA Chemical Indutries, Ltd.

17-85 Jusohonmachi 2-chome,

Yodogawa-ku, Osaka, Japan

ATTACHMENT 15-7

Certificate of Environmental Compliance from the Mayor of Fujisawa City for the Manufacture of Drug Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg)

Environmental Assessment

To whom it may concern:

This is to affirm that Shonan Plant of Takeda Chemical Industries, LTD. of which facilities are to manufacture Lupron Depot 3 Month 11.25 mg (drug product and vehicle), complies with applicable local Kanagawa Prefecture and Japanese national environmental regulations on air and water pollution control.

Date Nov. 21, 1995

Signed by

Shun Hayama

Shun Hayama

Mayor of Fujisawa City

ATTACHMENT 15-8

Certificate of Environmental Compliance from the Director of Shonan Plant, Fujisawa City, Japan

TAKEDA CHEMICAL INDUSTRIES, LTD.

HEAD OFFICE

ESTABLISHED 1781
INCORPORATED 1925

Fax:
(06)204-2244
Telex.
J63404
TAKEDA J63404

TOKYO OFFICE : Nihonbashi Chuo-ku Tokyo

O S A K A
3-6 Doshomachi 2-chome Chuo-ku

Environmental Assessment

To whom it may concern:

This is to confirm that manufacturing of Lupron Depot 3 Month 11.25mg (drug product and vehicle) complies with all applicable local Kanagawa Prefecture and Japanese national environmental regulations.

Date November 27, 1995

Signed by

Shin-ichiro Hirai

Director of Shonan Plant
Takeda Chemical Industries, Ltd.

2-26-1 Muraoka Higashi, Fujisawa City,
Kanagawa, Japan

APPENDIX A

Material Safety Data Sheets

MATERIAL SAFETY DATA SHEET

ABBOTT LABORATORIES
CHEMICAL & AGRICULTURAL PRODUCTS DIVISION
NORTH CHICAGO, ILLINOIS 60064
EMERGENCY TELEPHONE 1-708-937-6100
CHEMTREC 1-800-424-9300

ISSUE DATE:08/19/94 TSCA STATUS:Exempt APPROVAL:_____

LIST/CODE:5375,5508,3626/41450, 41558,41559

PRODUCT NAME: Leuprolide Acetate

CHEMICAL NAME: 6-D-Leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamideluteinizing hormone-releasing factor monoacetate; $C_{61}H_{88}N_{16}O_{14}$

DOT CLASSIFICATION: Not Regulated

HAZARDOUS INGREDIENTS/IDENTITY INFORMATION

NAME (CAS NO.)	OSHA PEL	ACGIH TLV	ABBOTT LIMIT	%
Leuprolide Acetate*(74381-53-6)	NL	NL	**	

*=Hazardous per OSHA criteria

** = Internal Guideline 0.01 mcg/ml (8-hr TWA). In the event that the exposure limit cannot be demonstrated by air monitoring, biological monitoring to assess exposure (specific program designed and administered through Corporate Employee Health) should be used.

PHYSICAL PROPERTIES

Appearance: white, flocculant powder

Solubility: Completely soluble in water

Boiling Point: N/A
Melting Point: N/D
pH: N/A
Vapor Pressure: N/A
Vapor Density: N/A
Density: N/A
Viscosity: N/A

FIRE AND EXPLOSION DATA

Flash Point: N/A

PRODUCT NAME:Leuprolide Acetate

FIRE AND EXPLOSION DATA (cont)

Extinguishing Media: Use appropriate media for underlying cause of fire

Special Fire Fighting Procedures: Wear protective clothing and self-contained breathing apparatus

Unusual Fire and Explosion Hazards: N/D

REACTIVITY

Incompatibility: Hypochlorite solutions

Hazardous Decomposition or By-products: N/D

Conditions to Avoid: N/D

HEALTH HAZARD DATA

Routes of Entry: Inhalation - YES Skin - Yes Ingestion - Yes

Oral Toxicity: N/D. Oral administration has produced pharmacologic responses in men at a dose of 10 mg

Dermal Toxicity: N/D. LD50 > 100 mg/kg (SC) in rats and mice. Skin application has produced pharmacological responses in humans and animals.

Inhalation Toxicity: N/D. Intranasal application has produced pharmacologic responses in men and women at doses of 50 mcg or more

Corrosiveness: N/D

Dermal Irritation: N/D

Ocular Irritation: N/D

Dermal Sensitization: N/D

Special Target Organ Effects: In clinical use, subcutaneous doses of 1 mg/day act as potent, but reversible, inhibitors of GnRH secretion by the pituitary resulting in inhibition of ovarian and testicular function. In contrast, doses as low as 0.36 mcg or more stimulate gonadotropin release. In rabbits, subcutaneous dosages as low as 0.1 mcg/kg/day produced embryolethality while dosages of 10 mcg/kg/day produced fetal resorptions in rats. Materials similar to leuprolide have the potential to exert a contraceptive effect in pregnant women if administered 5-8 days after the LH surge.

Carcinogenicity: NTP - NL IARC - NL OSHA - NL ACGIH - NL

PRODUCT NAME:Leuprolide Acetate

HEALTH HAZARD DATA (cont)

Carcinogenicity (cont): Benign pituitary hyperplasia and tumors were found in carcinogenicity studies in rats (0.6-4 mg/kg/day). A study in mice at dosages up to 60 mg/kg/day was negative and noncomparable effect has been found in man at doses up to 20 mg/day

Signs and Symptoms of Exposure: N/D. In clinical use, the initial response to leuprolide acetate is an increase in LH, FSH and male and female sex hormones (e.g. testosterone and estrogens). Continued use leads to reductions in these hormones to castrate or post-menopausal levels. Other adverse reactions include hot flashes, edema, GI upset, dizziness, headache, bone pain, weakness.

Medical Conditions Aggravated by Exposure: N/D. Data suggest preexisting pituitary, ovarian or testicular dysfunction. Metastatic vertebral lesions and/or urinary tract obstruction

Emergency and First Aid Procedures: Remove from source of exposure. If skin or eye contact occurs flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. No known antidote. Provide symptomatic/supportive care, monitoring hormone/sexual function, as necessary

SPECIAL PROTECTION INFORMATION

Ventilation: Use inside hood or glovebox

Respirator: Supplied air respirator

Gloves: Wear 2 pair; Latex inside, thicker outside

Eye Protection: Full face respirator

Other Protection: Wear fullbody tyvek coverings with hood and shoe covers

SPECIAL HANDLING AND STORAGE

Special Precautions: Wash thoroughly after handling this compound. Keep latex gloves on until all potentially contaminated personal protective equipment is removed

Spill or Release Procedures: Wet material before cleanup to prevent dust generation. Utilize ventilation and personal protective equipment during cleanup. Avoid dust. Place in appropriate container for disposal. Ventilate and wash spill area.

Waste Disposal: Dispose of material in accordance with applicable federal, state, and local regulations

Other Handling: N/D

PRODUCT NAME:Leuprolide Acetate

Legend

N/A = NOT APPLICABLE
N/D = NOT DETERMINED
NL = Not Listed
L = Listed
C = Ceiling
S = Short Term
(R) = A registered trademark of Abbott Laboratories
(TM) = A registered trademark of Abbott Laboratories

APPENDIX B

References

B1. Akwete Lex Adjei and L. Hsu. Leuprolide and Other LH-RH Analogues. In Stability and Characterization of Protein and Peptide Drugs. Case Histories. Ed. Y. John Wang and Rodney Pearlman, Plenum Press, New York.

B2. Metcalf & Eddy, Inc. Wastewater Engineering: Treatment Disposal Reuse. Revised by G. Tchobanoglous. New York: McGraw-Hill Book Company.

B3. Naeshiro, S. Kondo, S. Mitani, K. Yoshida, H. Kobayshi, T. Kimura, S. Shimomura and S. Tanayama. Metabolic Fate of TAP-144, An LH-RH Agonist In Rats and Dogs. Japanese Journal of Therapeutics 18:35-56.

B4. Pharmaceutical Manufacturers Association (PMA), 191. Interim Guidance of the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. PMA, Washington, D.C.

B5. U.S. Food and Drug Administration. 1995. Guidance for the Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. FDA, Washington, D.C. *Reference not included.

B6. Literature Review of the Polymers of Lactic and Glycolic Acids.