

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S18

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

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

Zoladex 3.6 mg

Goserelin acetate implant

Subcutaneous Implant

NDA 19-726, S-018

**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 19-726, S-018

Zoladex 3.6mg

Goserelin acetate implant

Subcutaneous Implant

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 supplemental new drug application for Zoladex - 3.6mg, which was submitted to add a new indication as an endometrial thinning agent prior to endometrial ablation, Zeneca Limited has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

The drug substance and drug product will be manufactured by Zeneca Pharmaceuticals in Macclesfield, England. The finished drug product will be used in hospitals, clinics and physicians' offices.

Goserelin acetate, a peptide LHRH analog, is a biodegradable drug substance and is metabolized in vivo through the normal metabolic pathways. Any excreted metabolites will enter public water and sewage treatment facilities. Any manufacturing wastes will be discharged, after treatment at the manufacturing site, into public water treatment facilities. Disposal of the drug may result from out-of-specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Rejected, expired or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations.

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.

6/2/97

DATE



PREPARED BY

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

6/2/97

DATE

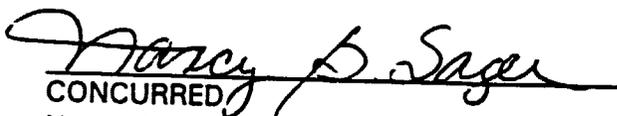


DIVISION CONCURRENCE

Moo-Jhong Rhee, Ph.D.
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6/5/97

DATE



CONCURRED

Nancy B. Sager
Environmental Assessment Team Leader
Center for Drug Evaluation and Research

Attachments: Environmental Assessment

cc:

Orig. NDA 19-726, S-018
HFD-580/Division File
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HFD-004/FONSI File 19-726, S-018
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**ZOLADEX® (goserelin acetate implant) sNDA
Endometrial Thinning Indication**

ITEM 3

D. Environmental Assessment - Nonconfidential Version

ZOLADEX

AS AN ENDOMETRIAL THINNING AGENT

PRIOR TO ENDOMETRIAL ABLATION

ENVIRONMENTAL ASSESSMENT

NON-CONFIDENTIAL VERSION

5/IF/US/1020805

ZOLADEX ENVIRONMENTAL ASSESSMENT

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SECTION 1. DATE:

May 1996

SECTION 2: APPLICANT

ZENECA Limited,
Macclesfield, Cheshire, England

ZENECA Inc. is the authorised US agent for ZENECA Limited for the subject NDA

SECTION 3. ADDRESSES: Administrative Headquarters.

ZENECA Pharmaceuticals Group
1800 Concord Pike
Wilmington, Delaware 19897

ZENECA Limited
Alderley Park
Macclesfield Cheshire
SK10 4TF England

Site for Formulation of Drug Product

ZENECA Limited
Macclesfield Cheshire
SK10 2NA England

US Distribution Centre

ZENECA Pharmaceuticals Group
1800 Concord Pike
Wilmington, Delaware 19897.

SECTION 4. DESCRIPTION OF THE PROPOSED ACTION

4.1 Describe the requested action

ZENECA Pharmaceuticals Group is filing an NDA suppliment for approval to market Zoladex 3.6mg as an endometrial thinning agent prior to endometrial ablation.

4.2 Describe the need for the proposed action

ZENECA is filing an NDA suppliment in which it is providing clinical data to support the use of Zoladex as an endometrial thinning agent prior to endometrial ablation.

This will be the fourth indication/efficacy claim for Zoladex; Zoladex 3.6 mg depot is currently approved in the US for the treatment of advanced prostate cancer (NDA 19-726 approved December 29, 1989) and the treatment of endometriosis (NDA 19-726/S-005 approved on February 2, 1993) and for the treatment of advanced breast cancer in pre and perimenopausal women (NDA 20-515 approved on December 18, 1995.)

Zoladex is a potent synthetic decapeptide agonist analogue of the naturally occurring hormone known as luteinizing hormone releasing hormone (LHRH). The compound differs from the naturally occurring hormone by virtue of substitutions made at positions 6 and 10 of the peptide chain: the chemical name for Zoladex is [D-Ser (But)⁶ Azgly¹⁰] LHRH.

In women, pretreatment with Zoladex 3.6 mg lowers estrogen levels and thins the endometrium prior to endometrial ablation, benefiting both the patient and surgeon.

4.3 Locations where the product is to be :

(1) Produced

The active drug substance will be formulated at the ZENECA manufacturing site at Macclesfield

The address of the facility is:-

ZENECA Limited
Charter Way, Hurdsfield Industrial Estate
Macclesfield, Cheshire, SK10 2NA. England

(2) Packed

Final packing will take place at Newark, Delaware in the USA.

The address of the Newark facility is :

ZENECA Pharmaceuticals Group
587 Old Baltimore Pike
Newark, Delaware 19711

The latter facility will be the distribution centre for the USA

(3) Used

Zoladex is used in hospitals, clinics and physicians' offices. Zoladex is administered by and disposed of by health care professionals.

(4) Disposed

Zoladex is administered in the form of an injectable depot. The packaging would be disposed of by the normal methods used for disposing of the packaging of medicinal products.

Any rejected, returned or time expired product will be disposed of by high temperature incineration in facilities approved by the relevant local authorities.

4.4 Types of location in which the manufacturing sites detailed in 4.3 (1) above are located.

4.4.1 Manufacture of the Drug Product

The ZENECA Pharmaceuticals site at Macclesfield is located in an area designated as an industrial zone. It is adjacent to other industrial properties and is bounded on one side by a residential area and on the other by farmland.

The site stands to the west of a range of hills on the edge of open country. The prevailing wind direction is from the south west.

The site itself is 82 acres of land which slopes from east to west. The site is located near the eastern edge of the Cheshire Basin. The Cheshire Basin contains Triassic sediments (approximately 225 - 190 million years old) which were deposited by very large north flowing braided rivers systems which flowed within fault controlled basins such as the Cheshire Graben during the Triassic Period. The Cheshire Basin was a subsiding structure which allowed the accumulation of several 1,000 metres of Triassic sediments. The gradual erosion and burial of the upland 'sediment source' areas during Triassic times led to a progressive change in the type of sedimentation. Early peidmont delta deposits gave way to water-lain sands and eventually to marls deposited in standing water. Thus, in general, deposits of progressively finer grain were laid down as the Triassic period continued.

Approximately 1 km to the east of the ZENECA site is located the north-south trending Red Rock Fault, which represented the former edge of the Triassic depositional basin. To the east of this fault lie the high grounds of the Peak District which comprise Carboniferous strata, notably the Millstone Grit Series in the vicinity of Macclesfield.

The Cheshire Basin Triassic Sandstone lithologic sequence comprise the Bunter and Keuper Formations. The Bunter Formation attains a thickness of nearly 1,000m and characteristically comprises soft red and mottled sandstone. The three sub-divisions of the Bunter are:

- Upper Mottled Sandstone;
- Bunter Pebble Beds;
- Lower Mottled Sandstone.

All are heavily stained with ferric oxide giving them their brick red coloration. The Bunter pebble Beds which are characteristically more indurated and coarser grained than the Mottled Sandstones are particularly thick in the Cheshire Basin.

The Keuper Formation overlies the Bunter and in most areas the basal Keuper is sharply differentiated from the underlying formation, being a hard, coarse grained sandstone. The Keuper Formation is over 1,250m thick in the Cheshire Basin and is made up of a three-fold division:

- Keuper Marl;
- Waterstone;
- Keuper Sandstone (bottom).

All three groups merge into one another becoming progressively finer in grain until the clay of the Keuper Marl, with its evaporitic beds, overspread the other Triassic rocks. In the Alderley Edge area, the Keuper Sandstone basal beds are noted as being coarse grained and conglomeratic. The Waterstones are an alternating series of thin bedded marly brown sandstones and soft sandy marls and variegated shales. They represent a transitional depositional phase between the underlying Keuper Sandstone and the overlying Keuper Marl. In the Cheshire Basin the Keuper Marl attains its fullest development in Britain. The Keuper Marl comprises a relatively homogeneous sequence silty red clay (Marl) with thin intercalations of dolomitic substance.

In the vicinity of the ZENECA Macclesfield site the Triassic Sandstone lithologies comprise Upper Mottled Sandstone and Bunter Pebble Beds of the Bunter Formation, and no impermeable Keuper lithologies are present.

Overlying the Triassic Sandstone Formations are a sedimentary succession of Pleistocene and recent deposits, which are 50-60m in thickness in the vicinity of the ZENECA Macclesfield facility. These drift deposits are generally differentiated as boulder clay or sands and gravels. This is somewhat misleading as they are characteristically intricately intercalated with both vertical and lateral gradation and discontinuity.

The site has been developed over the last 20 years to provide a comprehensive facility for the development, manufacture, formulation and distribution of pharmaceuticals together with associated laboratories and administration areas. The buildings are of modern design and construction.

4.4.2 Final packing and Distribution

Geographically the ZENECA Pharmaceuticals Group facility is on the Delaware Peninsula where the weather is moderated by both the Chesapeake Bay to the west and the Delaware River and Bay and Atlantic Ocean to the east. The area of the plant site is a plain just south of hills which extend from northern Delaware into Pennsylvania.

The environment of the site itself is 87 acres of relatively flat second growth woodlands. The soils are a thin layer of organic soils over heavy clay and occasional sand or glacial till. The sedimentary rock beneath the soils is deeply buried at the plant site and nearby area. Development of the site is about 405,000 square feet of buildings which supports the pharmaceuticals business, substantial grass lawn areas and decorative plantings, paved walkways, paved and unpaved access roads, and paved parking lots. The buildings are of modern construction, designs and materials and have been built specifically for pharmaceuticals production since 1971. Site drainage improvements have been made by installing a pond to slow rainwater run-off from buildings and paved areas.

The environment adjacent to the site is to the north, US interstate 95; to the west a casement for an interchange to US interstate 95; to the south, Old Baltimore Pike and a residential area; and to the east, Salem Church Road and a residential area.

The potable water is supplied by _____ and the waste water from the site is treated in the New Castle County Municipal Sewer System at the Wilmington Treatment Facility.

5.0 IDENTIFICATION OF CHEMICALS SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

The following is information relating to:

5.1 Nomenclature and description including structural formula for goserelin acetate

5.2 Description of the synthetic route

Confidential

5.3 Impurities arising from the synthesis of goserelin acetate by Macclesfield

Confidential

A complete disclosure of the manufacturing process was previously reported in the applicants approved NDA for Zoladex, No 19-726, submitted on August 14, 1987 and was approved by the agency on December 29, 1989. The information was updated in the 1994-5 Annual Report.

5.1 Active Constituents – Scientific Data

5.1.1 Nomenclature

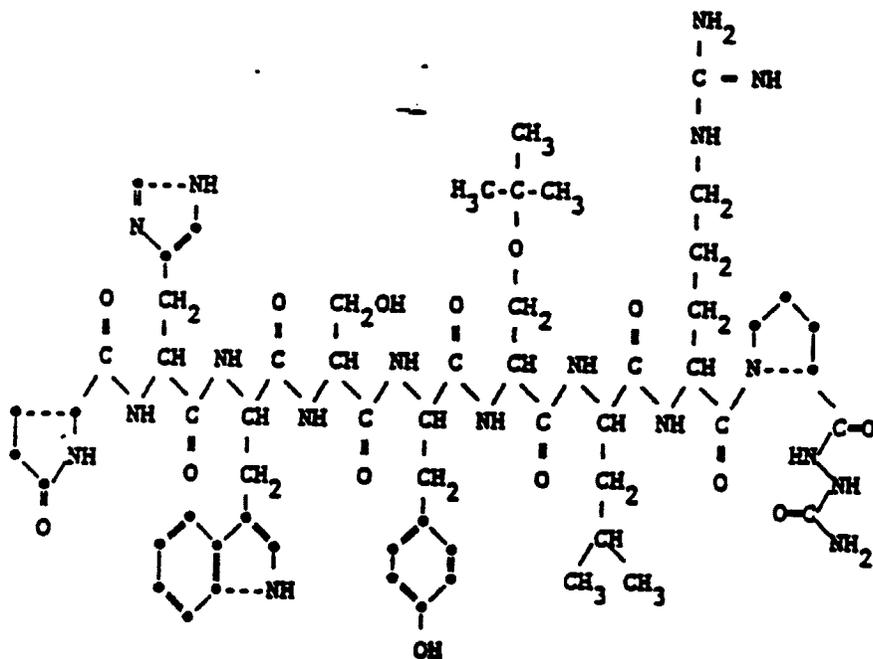
British Approved Name	:	Goserelin (base)
International Non-Proprietary Name	:	Goserelin (base)
U.S Adopted Name	:	Goserelin (base)
Laboratory Code Name	→	ICI 118,630 acetate
Chemical Name (base)	:	L-pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-(O-tert-butyl)seryl-L-leucyl-L-arginyl-L-prolyl-azaglycine amide
Abbreviated Chemical Name (base)	:	L-Glp-L-His-L-Trp-L-Ser-L-Tyr-D-Ser(Bu ^t)-L-Leu-L-Arg-L-Pro-AzGlyNH ₂ .
Proprietary Name	:	'Zoladex'
Other Names	:	6-D-(O-tert-butyl)serine-10-azaglycine amide-LH-RH, acetate salt.

(LH-RH is luteinizing hormone-releasing hormone)

5.1.2 Description

Physical form	:	A white to off-white powder
Molecular formula	:	C ₅₉ H ₈₄ N ₁₈ O ₁₄ (base)
Molecular weight	:	1269 (base)

Structural formula (base) :



SECTION 6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 From Production of Zoladex

The statements in Section 6.1 through 6.4.2 refer to the facilities in the UK which produce both the active agent and the drug product. Section 6.5 refers to the final packing facility which is located in the US as stated in Section 4.3.2.

All production of active pharmaceuticals on the Macclesfield Site is authorised by Her Majesty's Inspectorate of Pollution (HMIP) under the terms and conditions of the Environmental Protection Act and Integrated Pollution Control (IPC). This requires that the site, as well as meeting all current operating consents and conditions, to employ the Best Available Techniques Not Entailing Excessive Costs (BATNEEC) to minimise all discharges to the environment. It is also required to utilise the Best Practical Environmental Option (BPEO) in minimising and disposing of wastes.

The Authorisation is numbered AK 4079 and the site's performance is continuously monitored by HMIP. Permission for the site to be allowed to continue to operate is dependant on continuing compliance with all the terms of the Authorisation

6.1.1 Aqueous Arisings from Manufacture of Zoladex

Aqueous Layers from the production of the formulated product are combined in the sites effluent collection/ treatment system. The total effluent from the site is settled to remove solids and the pH adjusted to between 6.0 - 9.5 before being discharged to a sewage treatment facility owned and operated by the

All discharges to this facility are made under an agreement between ZENECA and the North West Water Authority, who were the predecessors to
dated 24th September 1975.

6.1.2 Major Requirements of the Agreement

Flow	1.2 million gallons/day up to a maximum of 7 million gallons /week.
COD	88,200 lbs / week
Total Solids	500mg/litre
pH	6.0 - 9.5

6.1.3 Emissions of Zoladex

It is estimated that less than 10g/year will be emitted to wastewater systems as a result of production of the formulated material.

6.2 Air Emissions

6.2.1 Control of Air Emissions

All air emissions from the manufacturing facilities are in compliance with local and national legislation .

Emissions from "ZOLADEX" production are discharged in such a manner as to comply with local legislation. Where appropriate emissions are discharged through scrubbers or high efficiency filters.

Monitoring to ensure compliance is carried out where appropriate.

6.3 Non-aqueous Liquid Wastes

6.3.1 Treatment of Non-aqueous Liquid Wastes from the Production of Zoladex.

Non-aqueous liquid wastes are segregated where possible into separate components. These components are transported to specialised operators for recovery for non-pharmaceutical use. Where segregation and recovery is not feasible the streams are collected together in a common site system for high temperature incineration in a licensed facility off-site.

In this facility a destruction efficiency of >99.99% is assumed for all organic species. The flue gasses are treated to remove pollutants prior to discharge to atmosphere. The treatment consists of rapid quenching of the stream to minimise secondary reactions followed by wet scrubbing and particulate removal.

The facility meets all relevant operating and discharge permits

All contractors are regularly audited by ZENECA.

6.4 Solid Waste

6.4.1 Treatment of Solid Waste Arisings from Production of "ZOLADEX"

All solid wastes are collected as part of a site-wide system and stored temporarily, in appropriate containers, in a specially designated area. The storage and treatment of the wastes are controlled by a licence from the local waste disposal authority.

All organic wastes are transported, by licensed carriers, to an off-site facility for high temperature incineration.

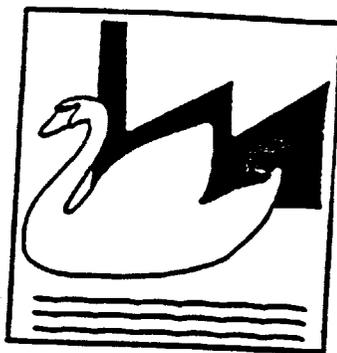
In this facility a destruction efficiency of >99.99% is assumed for all organic species. the flue gasses are treated to remove pollutants prior to discharge to atmosphere. The treatment consists of rapid quenching of the stream to minimise secondary reactions followed by wet scrubbing and particulate removal. The facility meets all relevant operating and discharge permits.

All contractors are regularly audited by ZENECA.

6.4.3 Permits for the Production Site

- A Site Authorisation AK 4079**
- B Waste Disposal Licence 60909**
- C Trade Effluent Discharge Agreement**

Compliance Statement by ZENECA Pharmaceuticals



HER MAJESTY'S INSPECTORATE OF POLLUTION

ENVIRONMENTAL PROTECTION ACT 1990

**Authorisation
and
Introductory Note**

Zeneca Pharmaceuticals

**Hurdsfield Industrial Estate
Macclesfield**

Authorisation Number AK4079

(Established Products)

Authorisation AK4079

page i of iii

17 March 1994

INTRODUCTORY NOTE

- IN 1. This Note does not form part of the Authorisation.
- IN 2. The following Authorisation is issued under section 6 of the Environmental Protection Act 1990 ("the 1990 Act") to operate a chemical process. The Authorisation comprises Part 1 (operation of the process, records and notifications), Part 2 (releases into air), Part 3 (releases into controlled waters), Part 4 (releases into sewer), Part 5 (releases into on-site effluent treatment plant), Part 6 (other releases from the process), Part 7 (reporting requirements), Part 8 (improvement programme), Part 9 (interpretation), Schedule 1 (notifications in accordance with condition 1.13), Schedule 2 (reporting of monitoring data), Schedule 3 (reporting of annual releases).

The Authorisation is subject to the express conditions set out in Parts 1 to 9. Aspects of the process not regulated by those conditions are subject to a general condition implied by section 7(4) of the 1990 Act that the person carrying it on must use the best available techniques not entailing excessive costs:-

(a) for preventing the release of substances prescribed for any environmental medium into that medium or, where that is not practicable by such means, for reducing the release of such substances to a minimum and for rendering harmless any such substances which are so released; and

(b) for rendering harmless any other substances which might cause harm if released into any environmental medium.

Techniques include (in addition to technical means and technology) the number, qualifications, training and supervision of persons employed in the process and the design, construction, lay-out and maintenance of the buildings in which the process is carried on.

IN 3. Description of Process

This process is for the manufacture of not more than 250 tonnes per year of purified bulk drug. This is achieved by the conversion of raw materials, often in multi-stage synthetic sequences to intermediates, crude bulk drug and the final purified bulk drug. The following drug series are produced from the raw material stage: Tamoxifen, Primidone, Lisinopril, 176334, 204219, D1033, Proguanil and Viloxazine. In addition the following pure drugs are produced by the purification and milling of crude bulk drug material manufactured elsewhere, Chlorhexidine Acetate, Chlorhexidine Hydrochloride and 204636.

Production takes place in the following designated buildings and plants, No.1 Building, Special Reactions Plant, Chemical Hydrogenation Plant and No.2 Purification Plant. Product stages are allocated to clearly defined units, with each unit accommodating one or more manufacturing stages. Manufacture is on a campaign basis with the required number of batches being produced in accordance with planning requirements.

Any new product to be manufactured within the areas specified above must fall within the scope of this authorisation and application, or an application for variation to this authorisation will be required.

Gases evolved from the process are passed through the appropriate wet scrubber. There are 4 scrubbers:

- No.1 Building Crudes Area - to remove ammonia and dimethylamine.
- No.1 Building Crudes Area - to remove acid gases
- Special Reactions Plant - to remove acid gases
- Bulk Corrosive Storage Area - to remove acid gases

In total there are a hundred and one vents associated with Volatile Organic Compounds (VOC) releases. In general each reactor vent has an on line condenser to minimise loss of VOC to atmosphere.

Charging of solid raw materials to vessels is carried out under extraction and through filters to atmosphere to minimise dust release.

The following operations which are related to the "pilot" plant process and this process are considered as part of this authorisation: bulk storage and handling of solvents and corrosives, storage of raw materials, on site treatment of aqueous effluent, works trade effluent plant, discharge to controlled waters and the storage of waste materials prior to disposal.

Process effluent is discharged to the strong aqueous effluent system, the bulk incineration system or a segregated receiver. The route to be taken is clearly identified on the process batch sheet. The effluent from the bulk incineration tanks is sent off site for incineration or use as support fuel, effluent from the segregated receiver is sent off site for specialist disposal. The effluent from the strong aqueous system receives pH adjustment, light and dense phase removal and is sampled prior to transfer to the buffer tanks. The sample is analysed to determine the dissolved Chemical Oxygen Demand (C.O.D) and to check the pH, provided the results are acceptable the buffer tanks discharge to the trade effluent drain. The trade effluent is collected in balancing tanks and allowed to settle prior to pH adjustment and discharge to sewer. The Company hold N W Water consent to discharge dated 24 September 1975 and amendments dated 26 March 1986 and 20 September 1976.

There is not normally a discharge into controlled waters, however under heavy rainstorm conditions a diverter redirects the excess surface water flow into Shoresclough Brook, a tributary of the River Bollin. The Company do not hold a consent to discharge with the NRA.

Inferior quality intermediate and crude bulk drug together with filtration media is stored in the designated Waste Storage areas prior to being sent off site for incineration.

HER MAJESTY'S INSPECTORATE OF POLLUTION
ENVIRONMENTAL PROTECTION ACT 1990

Authorisation

Zeneca Ltd

Authorisation No. AK4079

The Chief Inspector, in exercise of his powers under section 6 of the Environmental Protection Act 1990 ("the 1990 Act"), hereby authorises

Zeneca Ltd ("the Operator")

whose Registered Office is --

Imperial Chemical House
9 Millbank
London SW1P 3JF

to carry on a chemical process prescribed in Section 4.2 of Schedule 1 to The Environmental Protection (Prescribed Processes and Substances) Regulations 1991 ("the Authorised Process") at the premises occupied by the Operator at

Zeneca Pharmaceuticals
Macclesfield Works
Hurdsfield Industrial Estate
Macclesfield
Cheshire SK10 2NA

subject to the conditions in this Authorisation.

This Authorisation shall have effect from 24 March 1994

Signed

K W Murray

Dr K W Murray

(Authorised to sign on behalf of the Chief Inspector)

Dated the

17/3/94

Authorisation AK4079

page 1 of 21

17 March 1994

PART 1

OPERATION OF PROCESS

- 1.1 The Authorised Process shall, subject to the provisions of this Authorisation, be carried on using the techniques and in the manner described in the Application.
- 1.2 The Operator shall maintain in good operating condition all plant, equipment and technical means used in carrying on the Authorised Process.
- 1.3 The Authorised Process shall be managed and operated by sufficient persons who are suitably qualified, experienced, trained and supervised in respect of the duties to be undertaken in connection with the carrying on of the process.
- 1.4 The Operator shall provide the persons mentioned in condition 1.3 with appropriate written operating instructions for their duties in relation to the carrying on of the Authorised Process.
- 1.5 Any person having duties which are or may be affected by the matters set out in the Authorisation shall have convenient access to a copy of this document kept at or near to the place where he carries out those duties.
- 1.6 As a minimum, representative samples shall be taken and analysed in accordance with the methods, locations and frequencies specified in Table 1.1 and reported to the Chief Inspector.

SUBSTANCE	SAMPLING LOCATION	FREQUENCY OF SAMPLING	METHOD OF SAMPLING
Hydrogen Chloride mg/m ³	Release point numbers A2, A3 and A4 - as given in Table 2.1	6 monthly	Method to be agreed with the Chief Inspector
Oxides of Sulphur (expressed as sulphur dioxide) mg/m ³	Release Point numbers A2 and A3 - as given in Table 2.1	6 monthly	Method to be agreed with the Chief Inspector
Ammonia mg/m ³	Release point number A1 - as given in Table 2.1	6 monthly	Method to be agreed with the Chief Inspector
Anisole kg/hr	Release point number A8 - as given in Table 2.1	Annual	Method to be agreed with the Chief Inspector
Particulate mg/m ³	Release point A5 - as given in Table 2.1	Annual	Method to be agreed with the Chief Inspector
Active ingredient mg/m ³	Release points A6 and A7 - as given in Table 2.1	6 monthly	Method to be agreed with the Chief Inspector

HER MAJESTY'S INSPECTORATE OF POLLUTION

- 1.7 A safe means of access shall be provided to sampling and monitoring points when required by the Chief Inspector.
- 1.8 The Operator shall, subject to the provisions of this Authorisation, take such samples and carry out such analyses, calibrations, examinations, measurements, tests and surveys as are specified in the Application and at the frequency and in the manner so specified.
- 1.9 Subject to the provisions of this Authorisation, any assessment of analytical or monitoring results in relation to compliance with specified limits or operational parameters shall have regard to any provisions in the Application relevant to that assessment.

RECORDS

- 1.10 The Operator shall make a record of all samples, analyses, calibrations, examinations, measurements, tests and surveys taken or carried out as required by condition 1.8 ("specified records") and of any assessment made in accordance with condition 1.9.
- 1.11 The Operator shall make available for inspection by the Chief Inspector at any reasonable time -
 - (a) specified records;
 - (b) any other operational records made by the Operator in the course of carrying on the process ("operational records").
- 1.12 Specified records and Operational records shall:-
 - (a) be legible;
 - (b) be made as soon as reasonably practicable;
 - (c) if amended, be amended in such a way as to permit, where practicable, retrieval of the original record;
 - (d) be retained, in the case of specified records for a period of four years from the date when the records were made and in the case of operational records for a period of two years from the date when the records were made.

NOTIFICATIONS

- 1.13 The Operator shall notify the Chief Inspector:-
 - (a) of the detection of the release of any substance which exceeds any relevant limit or criteria specified in relation to the substance in this Authorisation;

HER MAJESTY'S INSPECTORATE OF POLLUTION

(b) of the detection of the release of any other substance which might cause harm except in a quantity so trivial that it would be incapable of causing harm or its capacity to cause harm is insignificant;

(c) of any malfunction or breakdown of plant, equipment, technical means or technology if the malfunction or breakdown has potential to cause serious pollution of the environment.

1.14 Notification under condition 1.13 shall be made *without delay* to the Reporting Address. In the case of a release mentioned in condition 1.13 (a) or (b) the Operator shall within 24 hours of such notification, send to the Reporting Address in writing the information set out in Part A of Schedule 1 and, as soon as practicable thereafter, the information set out in Part B of that Schedule.

1.15 If a release mentioned in condition 1.13 (a) or (b) is into controlled waters the Operator shall, *without delay*, also inform the National Rivers Authority of the release at its emergency telephone number published in the British Telecom local telephone directory.

PART 2

RELEASES INTO AIR

2.1 A release from the Authorised Process into the air from a release point specified in Table 2.1 shall arise only from the source for that release specified in that Table.

TABLE 2.1	
Release Point Number	Source
A1	No.1 Building - Crudes Area - Ammonia Scrubber
A2	No.1 Building - Crudes Area - Acid Scrubber
A3	Special Reactions Plant - Scrubber
A4	Bulk Corrosive Storage Area - Scrubber
A5	Outlets from laminar flow booths associated with raw material solids handling
A6	Particulate outlets associated with intermediate and finished product releases, including the milling areas.
A7	Air Extraction from No.1 Building - Pures Area
A8	No.1 Building - Pures Area and Crudes Area - vents associated with emission of anisole.
A9	Registered V.O.C. vents, other than those vents covered under release point number A8, from No.1 Building, Special Reactions Plant, Chemical Hydrogenation Plant and No.2 Purification Plant.

2.2 A release from the Authorised Process into the air from a release point specified in Table 2.2 shall not exceed the limit for that release point in relation to any parameter specified in that Table.

Parameters	Release Point								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Hydrogen Chloride mg/m ³		10	10	10					
Oxides of Sulphur (expressed as sulphur dioxide) mg/m ³		300	300						
Ammonia mg/m ³	15								
*Active ingredients mg/m ³	0.15	0.15	0.15			see Part 8	see Part 8		
Particulate mg/m ³					see Part 8				
Volatile Organic Compounds (expressed as toluene) tonnes/year									260
Anisole tonnes/year								24	

* "Active ingredient" is a material in a product, the properties of which are essential for the pharmaceutical application for which the product is designed.

2.3 Where a relevant annual mass limit is specified in Table A of Schedule 3, a release from the Authorised Process into the air shall not, in any year, exceed that limit.

PART 3

RELEASES INTO CONTROLLED WATERS

- 3.1 A release from the Authorised Process into controlled waters from a release point specified in Table 3.1 shall arise only from the source specified in and shall be released only into the receiving waters specified in that Table.

TABLE 3.1		
Release Point Number	Source	Receiving Waters
W1	Surface water - diverter	Shoresclough Brook

- 3.2 A release from the Authorised Process into controlled waters from a release point specified in Table 3.2 shall not exceed the limit for that release point in relation to any parameter specified in that Table.

TABLE 3.2	
Parameter	Release Point No. W1
None	-

- 3.3 There shall be no release from the Authorised process into controlled waters of any substance prescribed for water for which no limit is specified in Table 3.2 except in a concentration which is no greater than the background concentration.

PART 4

RELEASES INTO SEWER

4.1 A release from the Authorised Process into a public sewer from a release point specified in Table 4.1 shall arise only from the source specified in and shall be released only into the sewer specified in that Table.

TABLE 4.1		
Release Point Number	Source	Public Sewer
S1	On site effluent treatment plant	North West Water

4.2 A release from the Authorised Process into a public sewer from a release point specified in Table 4.2 shall not exceed the limit for that release point in relation to any parameter specified in that Table.

TABLE 4.2		
Parameter		Release Point No. S1
Cadmium	mg/l	1
Mercury	mg/l	1
Hexachlorocyclohexane	µg/l	1

4.3 There shall be no release from the Authorised Process into a public sewer of any substance prescribed for water for which no limit is specified in Table 4.2 except in a concentration which is no greater than the background concentration.

PART 5

RELEASES INTO ON-SITE EFFLUENT-TREATMENT PLANT

- 5.1 Provisions proposed in the Application with regard to releases to the effluent treatment plant have been assessed. No further specification of requirements is deemed necessary.

PART 6

OTHER RELEASES FROM THE PROCESS

- 6.1 The Operator shall have a written management procedure which in respect of all releases from the Authorised Process (including solid and liquid waste arisings) other than releases into the air, controlled waters, any on-site effluent treatment plant or any public sewer ("relevant releases") -
- (a) specifies the means by which compliance with the general condition implied by section 7(4) of the 1990 Act is achieved;
 - (b) ensures that those releases are handled, treated and disposed of in the most appropriate manner and that contamination of land is avoided; and
 - (c) specifies the means by which control of the process of accumulation and storage of any wastes on the site is achieved and includes the routes and timetable for disposal of wastes.
- 6.2 The Operator shall review the procedure mentioned in condition 6.1 and record the results of the review in writing -
- (a) whenever changes are made to the procedure which might have environmental significance; and
 - (b) in any case, not less frequently than once in every period of two years.
- 6.3 The Operator shall in respect of all relevant releases, record -
- (a) the composition, or as appropriate, the description of the release;
 - (b) the best estimate of the quantity of the release; and
 - (c) whether the release was recycled, disposed of or sold.
- 6.4 Materials arising from any relevant release from this process and any other authorised Part A process, shall only be stored on the site in the location and manner described in the Application.

PART 7

REPORTING REQUIREMENTS

- 7.1 The Operator shall, in respect of the parameters and release points specified in Table A in Schedule 2, report the results of such samples and analyses, calibrations, examinations, measurements, tests and surveys as are taken and carried out in accordance with condition 1.8. and of any assessment made in accordance with condition 1.9.
- 7.2 The reports mentioned in condition 7.1 shall -
- (a) be made for the reporting periods and on the forms specified in that Table; and
 - (b) be sent to the Chief Inspector at the Reporting Address within 28 days of the end of the reporting period to which the results refer.
- 7.3 The Operator shall by not later than 31 January in each year -
- (a) determine the best estimate of the total mass of each substance specified in Table A in Schedule 3 which was actually released during the preceding year; and
 - (b) send that estimate to the Chief Inspector at the Reporting Address on Forms S3/AR/1 set out in Schedule 3.
- 7.4 The Operator shall supply to the Chief Inspector at the Reporting Address on demand and without charge a copy of any specified or operational records as may be required.

PART 8

IMPROVEMENT PROGRAMME

The Operator shall complete the requirements specified in Table 8.1 by the date specified in that table and shall notify the Chief Inspector, at the Reporting Address, of the date of completion of those requirements.

TABLE 8.1		
Reference	Requirement	Date
8.1	The Company shall submit to the Chief Inspector its methods of sampling and analysis to support the sampling requirements given in Table 1.1.	30 Sept 1994
8.2	The Company shall carry out a feasibility study into reducing the emissions of anisole from release point number A8 to within the requirements of the Chief Inspectors Guidance Notes. The study and its findings shall be submitted to the Chief Inspector.	31 March 1995
8.3	The Company shall carry out a feasibility study into reducing the emissions of VOC from the release point number A9 to within the requirements of the Chief Inspectors Guidance Notes. The study and its findings shall be submitted to the Chief Inspector.	31 March 1995
8.4	The Company shall carry out monitoring to establish the concentration of particulate from release point number A5 and the concentration of active ingredient from release point numbers A6 and A7. If the results demonstrate that the particulate concentration is above 20 mg/m ³ and the active ingredient concentration is above 0.15 mg/m ³ , the Company shall submit proposals to the Chief Inspector, to reduce the emissions to within the concentration limits stated above.	31 March 1995
8.5	The Company shall carry out an investigation into the accuracy of the analytical method being utilised to measure the concentration of hexachlorocyclohexane in its discharge to public sewer and report its findings to the Chief Inspector.	31 March 1995
8.6	The Company shall carry out a programme of monitoring the concentration level of hexachlorocyclohexane in water supplied to the premises and water abstracted for use in the process and report its findings to the Chief Inspector.	31 March 1995
8.7	If the Company establish that the analytical method being utilised to measure hexachlorocyclohexane is accurate and that concentration levels of hexachlorocyclohexane discharged to public sewer are consistently above 0.5 µg/l, then the Company shall carry out a cleaning programme to remove as far as is practicable the residual hexachlorocyclohexane from the site drainage system.	30 June 1995

HER MAJESTY'S INSPECTORATE OF POLLUTION

8.8	The Company shall install standby circulating pumps on No.1 Building - Ammonia Scrubber and the Special Reactions Plant Scrubber.	30 April 1995
8.9	The Company shall install flow meters and low flow alarms in the circulating fluid lines of the No.1 Building Acid and Ammonia Scrubbers, Special Reactions Plant Scrubber and Bulk Corrosive Storage Area Scrubber.	30 April 1995
8.10	The Company shall install fan failure alarms for No.1 Building Acid and Ammonia Scrubbers and Special Reactions Plant Scrubber.	30 April 1995

PART 9

INTERPRETATION

- 9.1 In this Authorisation the following expressions have the meanings hereby assigned to them.
- "the Application" means the Application by the Operator dated 15 October 1993 and his response to any notices served under Schedule 1 to the 1990 Act; and any additional information supplied by the Operator in writing.
- "background concentration" has the same meaning as in Regulation 4(7) of the Environmental Protection (Prescribed Processes and Substances) Regulations (S.I.1991/472).
- "controlled waters" shall have the same meaning as in Part III of the Water Resources Act 1991;
- "public sewer" has the same meaning as in the Water Industry Act 1991;
- "release point" preceded by the letter A, W, E or S means respectively a point shown on a map or plan forming part of the Application for the release from the Authorised Process into the air, into controlled waters, into an on-site effluent treatment plant or into a public sewer.
- "Reporting Address" means the address, from time to time notified to the Operator, for that purpose by the Chief Inspector in writing; and for the purpose of this authorisation the first such notification is: HMIP, Unit 2, Kings Court, Manor Park, Runcorn, Cheshire WA7 1HR.
- "substance prescribed for water" means a substance prescribed by regulation 6(2) of the Environmental Protection (Prescribed Processes and Substances) Regulations (S.I.1991/472) and set out in Schedule 5 to those Regulations;
- "V.O.C." means Volatile Organic Compounds, which means all organic compounds released to air in the gas phase, expressed as toluene.
- "year" means calendar year.
- 9.2 References in any condition to a release not exceeding a limit shall, in relation to a limit expressed to be a minimum, mean that the release shall not be less than that limit.
- 9.3 No condition in this Authorisation applies so as to regulate or apply to the final disposal by deposit in or on land of controlled waste within the meaning of Part II of the Environmental Protection Act 1990.

HER MAJESTY'S INSPECTORATE OF POLLUTION

- 9.4 Unless otherwise stated, references to concentrations of substances in releases into air mean -
- (a) in relation to combustion gases, the concentration in dry air at a temperature of 273 K, at a pressure of 101.3 kPa and with an oxygen content of 3% dry for liquid and gaseous fuels, 6% dry for solid fuels.
 - (b) in relation to non-combustion gases, the concentration at a temperature of 273 K and at a pressure of 101.3kPa, with no correction for water vapour content.
- 9.5 Any reference to the notification of information on a form set out in Schedule 2 or 3 may be made on a form substantially to the like effect as the form referred to.

SCHEDULE 1

NOTIFICATIONS IN ACCORDANCE WITH CONDITION 1.13

Part A

Name of Operator.

Location of Process.

Date information provided.

Name[s] of the prescribed substance[s] or other substance[s] which might cause harm.

Time, date and location of the release.

Best estimate of the quantity of the substance[s] released or the rate of release and the time during which the release took place.

Environmental medium into which the release took place.

Measures taken, or intended to be taken, to stop the release.

Part B

Any more accurate information on the notification in Part A.

Measures taken, or intended to be taken, to prevent a recurrence of the incident.

Measures taken, or intended to be taken, to rectify any environmental damage which has been or may be caused by the release.

The dates of any unauthorised releases from the process which have taken place in past 2 years.

NOTE

(a) If any information supplied is considered confidential, a statement of which information this applies to and the reasons why must be specified.

(b) Units used in Part A and Part B shall be the same as those specified for similar releases in this Authorisation.

SCHEDULE 2

REPORTING OF MONITORING DATA

Parameters for which data shall be reported, in accordance with Part 7.1 of this Authorisation, are listed below.

The data should be submitted on forms included with this Schedule.

TABLE A			
PARAMETER	RELEASE POINT	REPORTING PERIOD	FORM NUMBER
Hydrogen Chloride	A2, A3, A4	12 months	S2/A3
Oxides of Sulphur (expressed as sulphur dioxide)	A2, A3	12 months	S2/A3
Ammonia	A1	12 months	S2/A3
Particulate	A5	12 months	S2/A3
Active Ingredients	A6, A7	12 months	S2/A3
Anisole	A8	12 months	S2/A3
Volatile Organic Compounds (expressed as toluene)	A9	12 months	S2/A3
Cadmium	S1	12 months	S2/W12
Mercury	S1	12 months	S2/W12
Hexachlorocyclohexane	S1	12 months	S2/W12

SCHEDULE 2

RELEASES INTO AIR - Release Summary for

Operator

Location

Authorisation Number **AK4079**

TABLE 7.A.3

Date	Release point(s)	Parameters						

Date.....Signed.....

(Table 2.2 Compliance)

Authorisation **AK4079**

SCHEDULE 3

LIST OF SUBSTANCES FOR WHICH ANNUAL MASS RELEASES ARE REQUIRED

Authorisation Number AK4079

(in accordance with Part 7.3 of this Authorisation)

The data should be submitted on forms included with this Schedule.

TABLE A			
SUBSTANCE	RELEASE POINT NUMBER	RELEASED TO	ANNUAL MASS RELEASE LIMIT/(tonnes) (where applicable)
Hydrogen Chloride	A2, A3, A4	AIR	-
Oxides of Sulphur (expressed as sulphur dioxide)	A2, A3	AIR	-
Ammonia	A1	AIR	-
Particulate	A5	AIR	-
Anisole	A8	AIR	24
Volatile Organic Compounds (expressed as toluene)	A9	AIR	260
Process effluent	Bulk incineration vessels	OFF SITE INCINERATION OR USE AS SUPPORT FUEL	-
Process effluent	Segregated Receiver	TREATMENT AND DISPOSAL OFF SITE	-
Out of Specification Intermediate and Crude Bulk Drug	Waste Disposal Compound	INCINERATION OFF SITE	-



**WASTE DISPOSAL LICENCE
NOTICE OF MODIFICATION**
*Control of Pollution Act 1974
Section 7*

Environmental Planning
Commerce House
Hunter Street
Chester CH1 2QW
Ian Gilfoyle *County Planning Officer*
Peter C Grainger *Chief Waste Regulation Officer*
Telephone (0244) 602424

Waste Disposal Licence No. --	60909
Name and address of licence holder	Imperial Chemical Industries Plc ICI Pharmaceuticals Alderley House, Alderley Park Macclesfield Cheshire SK10 4TF
Location of waste facility	ICI Pharmaceuticals Hurdsfield Industrial Estate Macclesfield, Cheshire, SK10 2NA.
	NGR SJ 925 755

In pursuance of its powers under the above Act, Cheshire County Council hereby give notice that the conditions relating to the above Waste Disposal Licence issued on 13th July 1989 are to be modified (in accordance with your application of 19th November 1991) as follows:

Conditions 1 - 35 shall now read as shown on the attached sheets.

Such modification shall take place on 12 March 1992 at 12.00 hours.

N.B. This licence only confers permission under Part 1 of the Control of Pollution Act 1974 and it is the responsibility of the licence holder to comply with the provisions of other legislation including the Town and Country Planning Acts, Health and Safety at Work, etc. Act 1974 and the Radioactive Substances Act 1960, where applicable.

Dated 12 March 1992
Signed PG
County Planning Officer

See overleaf for Statement of Rights of Appeal under Section 10 of the Control of Pollution Act 1974 as amended by the Collection and Disposal of Waste Regulations 1988 (S.I. 1988 No 819)

60909

12th March 1992

Licence No. Date

APPENDIX I

<u>WASTE TYPE</u>	<u>CODE</u>	<u>PHYSICAL FORM</u>	<u>M A X I M U M QUANTITY</u>
1. Aqueous Process Effluent	K93	Liquid	200 Tonnes
2. Solvent Process Effluent	K94	Liquid	140 Tonnes
3. Solvent Process Effluent (For Resale)	K84	Liquid	60 Tonnes
4. Process Waste In Drums	X10	Solid/Semi-Solid	20 Tonnes
5. Process Waste In Drums	K94	Liquid	14 Tonnes
6. Process Waste In Bulk Containers	X10	Solid/Semi-Solid	8 Tonnes
7. Packed Sales Stock	X11	Solid/Liquid	55 Tonnes

FOR ITEMISED DESCRIPTIONS OF THE VARIOUS EFFLUENT STREAMS SEE THE ATTACHED LIST APPENDIX III.

60909

12th March 1992

Licence No. Date.....

- 1 The area which is the subject of this site licence is shown outlined in blue on the attached drawing No M/01/B1051G FEB 89.
- 2 Storage and processing of special waste materials shall only take place within the areas outlined in red on the attached drawing No M/01/B1051G FEB 89.
- 3 The types and maximum quantities of special wastes permitted for storage are shown in the attached Appendix I and are itemised in the attached Appendix III. Only special wastes arising on the producers premises, as outlined in blue on the attached drawing No M/01/B1051G FEB 89, may be stored on-site.
- 4 Subject to the site licence conditions, the site shall be operated in accordance with the Working Plan attached to this licence as Appendix II and II(a).

SITE PREPARATION

- 5 Site control offices shall be located as detailed in the Working Plan Appendix II section ii) (c).
- 6 All tanks used to store special waste shall be located in areas constructed with impermeable bases and bund walls. The capacity of the banded areas shall be sufficient to contain, at all times, at least 110% of the volume of the largest tank situated within them.
- 7 Special waste storage areas for drums and/or bulk containers which contain semi-solids or liquids shall be constructed with impermeable bases and bunds as detailed in the attached drawing No M/02/E150168.
- 8 Boundary fencing, gates and access at the site shall be as detailed in the Working Plan Appendix II sections ii) (a) and (b).

WASTE STORAGE - OPERATION

- 9 The minimum levels of illumination within the special waste storage areas shall be maintained above:-
 - (i) 400 lux, measured at the instrument or control, where personnel are required to read or operate instruments or controls.
 - (ii) 200 lux, measured at ground level, where personnel are required to carry-out manual operations.
- 10 Subject to condition 9 the site may be operated 24 hours per day, 7 days per week.
- 11 Special wastes shall not be mixed or bulked in such a manner so as to give rise to uncontrolled reactions or the emission to atmosphere of noxious fumes or odours.
- 12 Special waste shall only be stored in containers of a construction and design suitable for the materials they contain.
- 13 The site shall be manned and supervised as detailed in the Working Plan Appendix II section iv) (b).

60909

12th March 1992

Licence No. Date.....

- 14 The boundary fencing and entrance gates shall be inspected daily with defects being repaired within 24 hours.
- 15 The bases and bunds of the drum, tank and bulk container storage areas shall be checked daily with any defects being repaired within 3 days.

STORAGE TANKS

- 16 All spillages within the storage tank banded areas shall be removed forthwith.
- 17 Each storage tank shall have the following :-
- (i) A contents gauge maintained in full working order
 - (ii) A clearly marked identification number as detailed in the Working Plan Appendix II section ii) (d).

DRUMMED SPECIAL WASTE

- 18 Incompatible wastes shall not be stored in the same storage bay. Each special waste storage bay shall be demarcated by:-
- (i) An impermeable bund wall, a minimum of 0.15 metres high or
 - (ii) When all drums containing special waste are stored on pallets, a 0.01 metre wide line of contrasting colour, marked on the base.
- 19 Drums containing special waste shall only be stacked in a secure manner.
- 20 All spillages within the drum storage area shall be removed forthwith.
- 21 All drums, within a storage bay, containing corrosive wastes shall be stored on pallets.
- 22 All drums containing special waste shall be sealed and stored in such a manner that the drum condition, identification markings and contents can be readily checked.
- 23 The special waste drum storage area shall be inspected at least daily to identify any leaking or damaged containers. Any such containers shall be removed and repackaged immediately.
- 24 Drums or bulk containers which contain special wastes which react adversely with water shall be stored under cover.
- 25 Drums containing more than 50 litres of waste material shall only be handled by mechanical equipment designed to handle such containers.
- 26 Special waste contained in drums shall not be stored on site for periods in excess of 6 months.
- 27 All drums containing special waste shall be labelled with an identification mark so that the waste type and the date of entry into storage may be determined.

Licence No. 60909 Date 12th March 1992

STORAGE OF SPECIAL WASTE IN BULK CONTAINERS

- 28 Special waste shall either be stored in enclosed skips or covered open topped containers.

MONO MUNCHER

- 29 The mono muncher shall be constructed as shown in drawing No. MO2/E/196776 and shall only be operated as detailed in appendix II(a).
- 30 Only liquid waste with a flash point greater than 30°C and any solid waste, shall be treated in the mono muncher.

RECORDS

- 31 A written record shall be made of the type and quantity (in tonnes) of all special waste, placed into or removed from storage, in each 24 hour period.
- 32 A summary of all special waste removed from storage shall be made annually. This record shall be forwarded to the Waste Disposal Authority, to arrive not later than by the 14th January of the subsequent year.

SITE OPERATION GENERAL

- 33 The terms and conditions of this site licence shall be made known to any person who is given responsibility for the management or control of the special waste storage facility.
- 34 A copy of this site licence shall be kept available in site offices as detailed in the Working Plan Appendix II section ii) (c).
- 35 This site licence shall remain in force until 13 July 1994 or until this licence is surrendered to the Waste Disposal Authority.

60909

12th March 1992

Licence No. Date

APPENDIX I

<u>WASTE TYPE</u>	<u>CODE</u>	<u>PHYSICAL FORM</u>	<u>M A X I M U M</u> <u>QUANTITY</u>
1. Aqueous Process Effluent	K93	Liquid	200 Tonnes
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5. Process Waste In Drums	X94	Liquid	14 Tonnes
6. Process Waste In Bulk Containers	X10	Solid/Semi-Solid	8 Tonnes
7. Packed Sales Stock	X11	Solid/Liquid	55 Tonnes

 FOR ITEMISED DESCRIPTIONS OF THE VARIOUS EFFLUENT STREAMS SEE THE
 ATTACHED LIST APPENDIX III.

Appendix II(a)

Mono Muncher

Type:

C14H065M/S3E2
Mono Pumps Ltd Muncher Division
7.5/11.0 KW 1440 rpm
Fitted with either 10 mm or 15 mm mesh
The Mono Muncher is fitted with a dust extraction system which is interlocked with the starter. A covered roller conveyor is used to transfer waste from the Quarantine Area and fire doors protect both areas from conflagration caused by tunnel effect. The Mono Muncher cannot be operated while the collection cabinet doors are open.

Duty:

The Mono Muncher is used to destroy the identity and integrity of sales packs and dosage forms. It will accept whole boxes without the need to unpack individual items. All solid formulations can be handled. Only liquid formulations having a flash point greater than 30°C are permitted to be passed through the Mono Muncher.

The maximum size of box which the machine can accommodate is 275 x 275 x 500 mm.

Location:

The Waste Disposal Area occupies a position on the eastside of the Macclesfield Site. It is located on two levels and is bounded by Site Roads R12 and R3. The Mono Muncher is located at the lower level adjacent to Road R12, while the upper level includes both internal and external Quarantine Areas.

Drainage Arrangements:

The Waste Disposal Area is serviced by drains which discharge into the Macclesfield Site trade effluent system. Spillages if not retrieved at source are contained in the trade effluent balancing tanks. The Shift Effluent Operator may be readily contacted by radio. Following treatment and/or discussion with North West Water Trade Effluent Inspectorate the contents of the balancing tanks may be discharged in a controlled way to the North West Water Effluent Treatment Works at Prestbury.

Trade Effluent discharge from the Macclesfield Site is controlled by a legally binding agreement with North West Water.

Storage Areas:

All waste arisings delivered to the Waste Disposal Area requiring pretreatment through the Mono Muncher are held in the internal Quarantine Area at the upper level of the Waste Disposal Area. The product from the Mono Muncher is collected in lined fibreboard kegs or drums and stored adjacent to the Mono Muncher at the lower level of the Waste Disposal Area (adjacent to Road R12) until an economic load has been accumulated.

1 Aqueous Process Effluent

The effluent will contain 1-3% acetone, 2-12% methanol, 1-5% ethanol and 0-5% other solvents such as n-propanol, isopropanol, n-butanol, isobutanol, and similar non-halogenated solvents eg trace of toluene, the balance being water. Neutralised acetic acid and formic acid will be present. Dissolved solids will be sodium chloride, sodium sulphate, pharmaceutical by-products and the sodium salt of p-toluene sulphonic acid.

2 Solvent Process Effluent

The effluent composition will vary depending on the manufacturing activity but the following solvents could be present in the effluent stream.

Trichloroethane
N-Butanol
N-Butyl Acetate
N-Hexane
Acetone
Acetonitrile
Chloroform
Cyclohexane
Dimethyl formamide
Ethyl Acetate
Ethyl benzene
Isobutanol
methylethylketone
Methylt-butylether
Methylene Chloride
Monochlorobenzene
Petroleum Ether 60-80
Sec Butanol
Solvent 20
Solvent 30
Solvent 60
Tetrahydrofuran
Toluene
White Spirit
Xylene
Ethanol
IMS
Isopropanol
Methanol
2-Methoxyethanol

3 Solvent Process Effluent
For Resale

The effluent will consist of aqueous IMS containing up to 60% IMS.

Process Waste in Drums
"Category 2"

The waste will consist of solids, tablets, capsules, spheroids and powders and will contain one or more of the following excipients and one or more of the following basic chemical ingredients.

"Category 3"

The waste will consist of fluid medicinal dosage forms, creams, ointments, gels and liquids and will contain one or more of the following excipients and one or more of the following basic ingredients.

Category 2 Basic Chemical Ingredients

Alprenolol Hydrochloride BP (Injection grade)
Ancasil (Stuart)
'Antrycide' Chloride, Quinapyramine Chloride B Vet C
'Antrycide' Methyl Sulphate, Quinapyramine Sulphate B Vet C
'Atromid' S Clofibrate
'Avloclor' Chloroquine Phosphate BP
'Avlosulfon' Dapsone BP
Avlothane Disp Powder
Bacitracin Zinc BP
Bendrofluazide BP
Benzocaine Ph Eur
'Cetavlon' Cetrinide Ph Eur
Chloroquine Sulphate BP
Chlorthalidone BP
Clioquinol BP (Chinoform)
Dapsone BP Powder
Dialose Capsules
Dialose Pluse
Diethyl Toluamide
Dihydro Streptomycin Sulphate BP (Vet)
Fluocinolone Acetonide BP ('Synalar')
Fluocinonide (Metosyn)
'Fulcin' Griseofulvin
Gamma Benzene Hexachloride BP
Gibberellic Acid
Gibberellins A4/A7
Gum Tragacanth
'Hibitane' chlorhexidine Acetate BPC
Chlorhexidine Hydrochloride BP
'Imperacin' Oxytetracycline
'Inderal' Propranolol Hydrochloride BP
Isothipendyl Hydrochloride BPC (Nilergex, Andantol)
'Lapudrine' Chlorproguanil Hydrochloride BP
Levanisole Hydrochloride
Louse Powder
Meprobamate (Mepavlon)

Mysoline Primidone BP
Neomycin Sulphate Ph Eur
Oxyclozanide B Vet C
Oxytetracycline Calcium salt
Oxytetracycline Dihydrate Ph Eur
Oxytetracycline Hydrochloride Ph Eur
'Paludrine' Proguanil Hydrochloride BP
Penicillin G Procaine
Penicillin V Potassium BP (Phenoxyethyl penicillin BP)
Phenothiazine
Phenytoin Sodium BP
Polymyxin B Sulphate Ph Eur
Povidone BPC
Povidone - Iodine USP
Primaquine Phosphate BP
Razoxim Razoxane
Sodium Nitrite
Spartakon
Streptomycin Sulphate Ph Eur
Sulphaguanidine BPC
'Sulphamezathine' sulphadimidine Ph Eur
'Tenormin' Atenolol
'Tetmosol' Monosulfiram
Tetramisole Hydrochloride B Vet C
'Vivalan' Viloxazine Hydrochloride

Excipients Include:

Acacia
Alginic Acid
Aluminium Hydroxide dried Gel MSP
Anti-foam
Beeswax
'Biostok' Urea Mineral
Brilliant Blue FCF Aluminium Lake
Calcium Carbonate
Calcium Carboxymethylcellulose
Calcium Chloride
Calcium Phosphate BPC
Camphorquinone
Carbopol 940
Carmine No 1
Carnauba Wax Yellow
Ceto Stearyl Alcohol
China Clay
Colophony BP
Disodium Edetate
Dispersed Dyes (various)
Edicol Dyes (various)

Empilans
Ethyl Cellulose Grade NSO
Eucalyptus Oil Ph Eur
Gelatin BP
Gelatin Byco C
Gluconolactone
Glucose
Glycerol
Glycol Dimethacrylate
Ground Limestone
Hydroquinone AR
Hydroxypropylmethly Cellulose
Iron Oxide
Kaolin
Lactose
Lissamine Fast Yellow
Magnesium Carbonate
Magnesium Hydroxide
Magnesium Stearate
Maize Mineral, Vitamin Supplement
Maize Starch
Malttrin 10
Malttrin 100
Mannitol
Menthol BP
Methanol
Methylated Spirits
Methyl Cellulose
Microcrystalline Cellulose BPC (Avical)
Opalux
Opacode, Inks (various)
Opaspray
Patent Blue V
Pharmacost
Povidone BPC
Powdered Vegetable Stearine
Primojel
Saccharin sodium BP
Shellac
Sodium Carbonate
Sodium carboxymethyl cellulose
Sodium Ethyl Hydroxybenzate BP
Sodium Hydroxide
Sodium Lauryl Sulphate (Empicol LZV)
Sodium metabisulphite
Sodium Propyl Hydroxybenzoate
Sodium Sulphite
Soflor Fresh Air Perfume
Sorbitan Monostearate (Span 60)
'Sorbitrate' Sorbide Nitrate

Starch
Stearic Acid BPC
Sucrose
Sugar, Confectioners
Synperonic
Talc
Tartaric Acid Ph Eur
Tartrazine
Thymol
Titanium Dioxide BPC
Topanol OC
Tragacanth
Vanillin Red Bond
Vinyl Silane
Vinyl Urethane

Category 3 Basic Chemical Ingredients

Antasil
Atromid S
'Avloclor' Chloroquine Phosphate BP
Bacitracin Zinc BP
Benzoin Tincture Compound BPC
'Cetavlon' Cetrinide BP
Chinoform (Clioquinol)
Diethyl Toluamide
Dimethyl Phthalate
Diothyl
'Epodyl' Ethoglucid
Fluocinolone Acetonide BP ('Synalar')
Fluocinolone ('Metosyn')
'Fulcin' Griseofulvin Ph Eur
Gamma Benzene Hexachloride BP
'Hibitane' Chlorhexidine Acetate BPC
Chlorhexidine Hydrochloride BP
Chlorhexidine Gluconate
'Inderal' Propranolol Hydrochloride BP
Iodophor Av (Iodine/Antarox)
Lapudrine Hydrochloride
Levamisole Hydrochloride
Levamisole Hydrochloride
'Mysoline' Primidone BP
Naseptin
Neomycin Sulphate Ph Eur
Oxyclozanide BP (Ver)
Oxytetracycline Calcium Salt
'Peptavlon' Pentagastrin BP
Steribath
'Sulphamezathine' Sulphadiazine Ph Eur

'Sulphamezathine' Sodium
'Tetmosol' Monosulfiram BP
Tetramisole Hydrochloride BP (Ver)
'Vivalan' Viloxazine Hydrochloride

Excipients Include

Acetone
Alcohol 95% BP
Amerchol CAB
Aminoxid WS 35
Ammonia (N/1)
Ammonyx LO
Aniseed Oil
Arachis Oil BP (Groundnut Oil)
Arcton II (Trichlorofluoromethane BPC)
Barium Sulphate
Benzyl Alcohol BP
Benzyl Benzoate BP
Borax Ph Eur
n-Butanol AR
Butylated Hydroxytoluene BP (Topanol OC)
Calcium Chloride
Carbopol 940
Caster Oil
Cetostearyl Alcohol BP
Citric Acid Ph Eur
Citronella Oil BPC
Cremopher RH 40
Deodoriser Liquid
Disodium Edetate BP
Dispersal OG
Edicol Dyes (Various)
Empilan CDE
Enythrosine
Eucalyptus Oil
Flavour (various)
Formaldehyde Solution
d-Gluconolactone
Glycerol Ph Eur
Herbacol
1:2:6 Hexanetriol
Hydroxypropyl Cellulose (Klucel HF)
Isopropanol
Kaolin
'Keltrol' Gum
Lanolin
Linalyl Acetate
Lissamines (dyes various)
Loramine

Lubrol
Menthol BP
Methylated Spirits
Methyl Hydroxybenzoate Ph Eur (Nipagin M)
Miranol
Natrosol
'Nipasept' (Methyl Ethyl Propyl Hydroxybenzoate)
Paraffin (liquid)
Perfumes (various)
Petroleum Jelly
Piperonyl Butoxide
Pluronic
Polyethylene Glycol
Polysorbates (Tweens)
Povidone BPC
Propylene Carbonate
Propylene Glycol Ph Eur
Propyl Hydroxybenzoated Ph Eur
Rhodamine B
Saccharine Sodium
Silicone Oil (Dimethicone BPC 1000) Dimethicone USNF
Sodium Acetate BP
Sodium Alginate (Manucol)
Sodium Carboxymethyl Cellulose
Sodium Chloride
Sodium Citrate Ph Eur
Sodium Cyclamate
Sodium Ethyl Hydroxybenzoate
Sodium Hydroxide
Sodium Lauryl Sulphate
Sodium Metabisulphite
Sodium Methyl Hydroxybenzoate BP (Nipagin M Sodium)
Sodium Propyl Hydroxybenzoate BP (Nipasol M Sodium)
Sodium Sulphite BPC
Sorbitans (Spans)
Sorbitol
Spike Lavender Oil
Stearic Acid BPC
Stearyl Alcohol
Synperonic
Talc
Terpineol BP
Terpinolene
Thiomersal BP
Tragacanth
Triethanolamine
Vanillin BPC
Beegum HV
Waxoline (dyes various)
White soft paraffin BP

5 Process Waste in Drums

The waste consists of a mixture of liquid effluents arising from the Laboratories Block and from Development Plants not linked to the Bulk Effluent Collection System. Composition is similar to stream 2.

6 Process Waste in Skips

The waste will consist of the following:

- a) the residue from a mono muncher and will contain fragmented plastic, aluminium, glass, cardboard and other packaging materials and will include category 2 and category 3 excipients and basic chemical ingredients.
- b) laboratory waste such as filter paper, broken glass, quantities of chemicals and excipients arising from experimental or analytical work but excluding cyanides, known carcinogens heavy metals and radioactive wastes.
- c) Category 2 and category 3 excipients and basic chemical ingredients.
- d) Carbon and filtration media
- e) Airfilters containing traces of pharmaceutical products.

General Waste in Skips

The waste will consist of salvage, cardboard, plastic and package components, which include; outers, cartons, sachet foil, divisions, collapsible tubes overwrap, instruction cards, uncontaminated glass and plastic bottles.

7 Packed Sales Stock
IQ and Out of Shelf-Life

The waste will consist of solid/liquid dosage forms and will contain category 2 and 3 basic chemical ingredients and excipients.

DTU

Alderley House Alderley Park
Macclesfield Cheshire
SK10 4TF

Telephone Alderley Edge (0625) 532228
Telex 669095/669388

*File
Macclesfield*



Imperial
Chemical
Industries
Limited

Pharmaceuticals
Division

Mr W H Crackle
Assistant Director, Legal Services
North West Water Authority
Dawson House
Great Sankey
Warrington
WA5 3LW.

Your ref	Ourref	Telex	Date
	MJO'B/MJH/SMT		9 March 1977

Dear Mr Crackle,

TRADE EFFLUENT AGREEMENT DATED 24 SEPTEMBER 1975

I should be grateful if you would accept this letter as ICI's notice to you that we wish to use the method of direct reimbursement provided for by Clause 4(c) (1) for Phase III of the agreed extension programme.

I should be grateful if you would acknowledge receipt by signing and returning the enclosed copy of this letter.

Yours sincerely,

M J O'Brien
Division Secretary

AGREED AS ABOVE

W.H. Crackle, Assistant Director, Legal Services
For and on behalf of North West Water Authority

Date *17th March 1977*

Alderley House Alderley Park
Macclesfield Cheshire
SK10 4TF

Telephone Alderley Edge (0996 6) 2228
Telex 669095/669388 (ICIPharm Aldley)
Telegrams Aviontex Macclesfield



Imperial
Chemical
Industries
Limited

Pharmaceuticals
Division

Mr. W. H. Crackle,
Assistant Director, Legal Services,
North West Water Authority,
Dawson House,
Great Sankey,
Warrington, WA5 3LW.

Your ref Our ref Tel ext Date
 MJO'B/MJH/ALB 20th September, 1976.

Dear Mr. Crackle,

TRADE EFFLUENT AGREEMENT DATED 24TH SEPTEMBER 1975

Clause 6(1)(d) of the above Agreement provides for a review of the factors in Clauses 6(1)(a) and (b). This review has taken place and I would accordingly propose that our Agreement is amended as from 24th September 1976 by replacing existing Clauses 6(1)(a) and (b) by the following:-

- *6. (1) As to strength
- (a) 63,420 lbs. C.O.D. per week (Monday 9 a.m. to Monday 9 a.m.) subject to peak load of 9,966 lbs. C.O.D. per day in any one day in the defined week until the said extensions are completed and thereafter
 - (b) 95,130 lbs. C.O.D. per week (Monday 9 a.m. to Monday 9 a.m.) subject to a peak load of 14,949 lbs. C.O.D. per day in any one day in the defined week."

As the review has not taken place entirely strictly within the time scales prescribed by existing Clause 6(1)(d), I propose that this Clause should now read as follows:-

"ICI and the Authority undertake to review the factor in the above formula at two year intervals from 24th September 1976. The C.O.D. loadings in (a) and (b) above will be modified as required by the formula using the mutually agreed factor."

If these proposals are acceptable to you would you please sign and return the enclosed copy of this letter.

Yours sincerely,

M. J. O'Brien;
Division Secretary

1110-11

25th October 1976

THE CLEEN'S AWARD

AN AGREEMENT made the *twenty-fourth* day of
September One thousand nine hundred and seventy-five
BETWEEN NORTH WEST WATER AUTHORITY whose principal
office is at Dawson House Great Sankey Warrington in the County
of Cheshire and their successors (hereinafter called "the
Authority") by WILLIAM HUGH CRACKLE its Solicitor and duly
authorised agent of the one part and IMPERIAL CHEMICAL
INDUSTRIES LIMITED whose registered office is situate at
Imperial Chemical House Millbank in the City of Westminster
(hereinafter called "I.C.I.") by MICHAEL JOSEPH O'BRIEN
their duly authorised agent of the other part

WHEREAS

- (1) I.C.I. are the owners of a factory site and premises on the
Hurdfield Industrial Estate Macclesfield (hereinafter called
"the Works") as is shown edged red on the plan attached hereto
- (2) I.C.I. discharge from the Works trade effluent and polluted
surface water being the surface water run off from an impervious
area of the Works (hereinafter together referred to as "the
Effluent") into the Authority's sewers
- (3) The terms and conditions upon which the Authority's
predecessors in title and the Authority have previously accepted
the discharge of the Effluent from the Works were contained in
an Agreement entered into under the powers contained in Section 7
of the Public Health (Drainage of Trade Premises) Act 1937 as
modified by the Public Health Act 1961 (hereinafter called "the
Acts") and made between the Mayor Aldermen and Burgesses of the
Borough of Macclesfield and I.C.I. which is dated the Fifteenth
day of October One thousand nine hundred and sixty-three
- (4) The Authority are desirous of carrying out extensions to
their Sewage Treatment Works at Butley Lane Prestbury (herein-
after called "the Treatment Works") and have agreed with I.C.I.
to allow in such extensions for an increased treatment capacity

in order to receive an increased volume and strength of the Effluent from the Works upon the terms and conditions hereinafter appearing

WHEREBY IT IS HEREBY AGREED as follows:-

1. THE Authority in exercise of their powers under the Acts and all other powers enabling them to do so hereby agree with I.C.I. that during the currency of this agreement I.C.I. may discharge into the Authority's sewers at the points of discharge marked A and B on the plan attached hereto (hereinafter called the said plan) all the hereinafter recited Effluent not exceeding the quantities set out in Clause 6 hereof
2. THIS Agreement shall replace the aforementioned Agreement dated the Fifteenth day of October One thousand nine hundred and sixty-three and shall come into force on the signing of this Agreement and shall continue in force until determination in accordance with Clause 3 hereof
3. THIS Agreement shall not be terminable by either party until such time as the capital referred to in Clause 4(a) and 4(c) hereof has been repaid and thereafter may be determined by six months' written notice by either party provided however that such notice of termination may not be given unless mutually acceptable alternative arrangements have been made for the reception and treatment of the Effluent
4. I.C.I. will pay to the Authority as follows:-
 - (a) Loan charges half yearly on the Thirtieth day of September and the Thirty-first day of March each year in respect of:-
 - (1) the proportion of the total design flow of fifty-eight million gallons per day attributable to the reservation of one point two million gallons per day for I.C.I. applied to the balance of the capital expended by the Authority's

predecessors in laying the sewer from
Beech Bridge to the Treatment Works

(2) the balance of the capital expended by
the Authority's predecessors together
with any capital yet to be expended by
the Authority on the One thousand nine
hundred and fifty-six and One thousand
nine hundred and sixty-one extensions
to the Treatment Works referred to in
the above recited Agreement dated the
Fifteenth day of October One thousand
nine hundred and sixty-three in the
proportion as is included in the Schedule
dated the Second day of November One
thousand nine hundred and seventy-two
prepared by Messrs. Mander Raikes and
Marshall a copy of which is annexed hereto

(3) In this clause loan charges means equal
half yearly instalments of principal
together with interest at the Authority's
average rate and management expenses
apportioned on the outstanding debt in
accordance with and as defined in the model
Institute of Public Finance and Accountancy
Consolidated Loans Fund scheme

(b) The Authority hereby undertake in consideration of
the payment of the instalments referred to in
Clause 4(a)(1) to reserve one point two million
gallons per day capacity in their main drainage
system for the reception of the Effluent from I.S.I.

(c) In respect of the capital to be incurred on the
proposed extension to the Treatment Works that
proportion as is included in the aforementioned

Schedule dated the Second day of November
One thousand nine hundred and seventy-two
prepared by Messrs. Mander Raikes and Marshall
either:-

- (1) direct reimbursement payment being made as expenditure is incurred by the Authority and instalments being paid within Twenty days of receipt of a certified account from the Director of Finance for the time being of the Authority or
 - (2) equal half yearly instalments on the Thirtieth day of September and the Thirty-first day of March each year of principal and interest together with management expenses for a period of twenty-five years from the end of the financial year in which the final capital payment is made the interest rate being the average rate of interest charged by the National Loans Fund for loans of Twenty-five years over the period of construction provided that during construction interest only at the average rate will be chargeable and the Authority shall provide I.C.I. with the best estimate of progress of the said extensions at reasonable intervals and with a budgeting programme on a quarterly basis
- (d) (1) Quarterly charges to cover the reception and treatment costs calculated on the current formula as set out in Clause 4(d)(2) (excluding from the calculation thereof any loan charges included in the calculation

of Clause 4(a) and 4(c) of the Effluent actually discharged by I.C.I. from the Works to the Treatment Works

(2) The aforesaid current formula is as follows:-

$$x = a + b \frac{(TOD^{te} - TOD^{fe})}{(TOD^{ss} - TOD^{fe})} + c \frac{(SS^{tes} - SS^{fe})}{(SS^{ms} - SS^{ic})}$$

Where:- x = total charge per One thousand gallons in pence

a = preliminary treatment cost per One thousand gallons of sewage received in pence

b = biological purification cost per One thousand gallons of average strength settled sewage in pence

c = sludge disposal costs per One thousand gallons of average strength sewage in pence

TOD = Total Oxygen Demand in mg/l

SS = Suspended Solids in mg/l

te = Trade effluent

fe = Final effluent

tes = Trade effluent (shaken)

ms = Mixed sewage

ss = Settled sewage

(e) Quarterly charges to cover the conveyance of the Effluent from the Works through the Authority's sewers to the Treatment Works calculated as detailed below on the actual cost of maintaining the sewers during the financial year ended Thirty first day of March. The actual cost shall be the ascertained gross expenditure for the year on or in connection with the repair and maintenance of such sewers together with capital charges rates and taxes on those sewers

conveying the Effluent and a reasonable proportion of the central administrative expenses after deducting all income specifically appertaining to such sewers but other than charges for the conveyance of trade effluent as certified by the said Director of Finance. The total flow passing through all sewers shall be the total for the year as received and recorded at the Treatment Works by the Officer appointed for that purpose by the Authority (hereinafter called "the Officer"). The calculation of the said charge in pence per one thousand gallons of the Effluent conveyed shall be as follows:-

$$V = \frac{(L + M)}{(Q)} \times 100 \text{ pence}$$

V = Charge in pence per One thousand gallons discharged

L = The total loan charges in pounds sterling for those sewers which carry the Effluent LESS all loan charges relating to the Beech Bridge Outfall Sewer

M = The revenue cost in pounds sterling of sewers carrying the Effluent to the Treatment Works including repair and maintenance rates taxes and insurance and a reasonable proportion of central administrative expenses less all income except that arising from charges for reception of trade effluent

Q = The total flow received at the Treatment Works in thousands of gallons per year as certified by the Officer

(f) The provisions of Appendix A to the Agreement shall apply for the purposes of calculating the charges to

be made in pursuance of Clause 4(d) and 4(e)
hereof

5. In respect of the payments to be made by I.C.I. under Clause 4(d) and 4(e) hereof the Authority will notify I.C.I. as soon as possible after the first day of April in each year the estimated charge for conveyance reception and treatment of the Effluent for the ensuing year and will render an account to I.C.I. as payments on account at the end of each quarter of the sum due in respect of the said conveyance reception and treatment during that quarter and such sum shall be payable by I.C.I. within Sixty days of the account being rendered. As soon as possible after the Thirty-first day of March a reconciliation account shall be sent to I.C.I. based on the actual cost and the appropriate adjustment to payments already paid on account shall be made

6. THE load upon the Treatment Works in respect of the Effluent shall not exceed

(1) As to strength

(a) 58,800 lbs. C.O.D. per week (Monday 9 a.m. to Monday 9 a.m.) subject to peak load of 9,240 lbs. C.O.D. per day in any one day in the defined week until the said extensions are completed and thereafter

(b) 83,200 lbs. C.O.D. per week (Monday 9 a.m. to Monday 9 a.m.) subject to a peak load of 13,860 lbs. C.O.D. per day in any one day in the defined week

(c) For the purposes of this Clause the calculation of the Chemical Oxygen Demand (C.O.D.) shall be except as modified by agreement between the Authority and I.C.I. as follows:-

$$\text{C.O.D. (in mg/l)} = \text{B.O.D. (in mg/l)} \times 1.4$$

(d) I.C.I. and the Authority undertake to review

the factor in the above formula within nine months of the Agreement coming into force and at further two yearly intervals. The C.O.D. loading in (a) and (b) above will be modified as required by the formula using the updated mutually agreed factor

(2) As to volume

- (a) 4.9 million gallons per week (Monday 9 a.m. to Monday 9 a.m.) subject to a peak load of 0.34 million gallons per day in any one day in the defined week until the said extensions are completed and thereafter
- (b) 7 million gallons per week (Monday 9 a.m. to Monday 9 a.m.) subject to a peak flow of 1.2 million gallons per day on any one day in the defined week

7. THE foregoing figure of volumetric load after the completion of the said extensions shall be subject to a maximum discharge of 62,500 gallons in one hour in any one day provide always that I.C.I. shall use their best endeavours to limit the rate of discharge to a total period of one half hour in any or day

8. (1) For the purpose of this Agreement the date of completion of the said extensions shall be construed as the date from which the Authority certifies to I.C.I. that the Treatment Works as extended are capable of accepting the Effluent specified in Clause 6(1)(b) and Clause 6(2)(b)

(2) During the period from the date hereof until the date of completion of the said extensions I.C.I. may discharge quantities of the Effluent in excess of the quantities set out in Clauses 6(1)(a) and 6(2)(b) in accordance with the availability of increased

capacity in the Treatment Works as certified by the Officer

9. (a) The composition and temperature of the Effluent passing through the drains marked "C" on the said plan shall comply with the following conditions:-
- (i) the temperature shall not exceed 43.5°C
 - (ii) the pH value shall not be less than 6.0 nor more than 9.5
 - (iii) the Effluent shall not contain (a) calcium carbide any degreasing solvent of the mono di or trichloroethylene type any product which produces under the conditions appertaining in the sewers inflammable vapour such as petroleum spirit any other volatile petroleum product or any inflammable solvent nor (b) yeast
 - (iv) the total solids in suspension including grease and oil shall not exceed Five hundred milligrammes per litre
 - (v) hydrocyanic acid and all compounds which produce hydrocyanic acid on acidification (expressed as HCN) shall not exceed One milligramme per litre
 - (vi) sulphides hydrosulphides and/or polysulphides (expressed as S) shall not exceed One milligramme per litre
 - (vii) water immiscible grease and oil shall not exceed Fifty milligrammes per litre daily average concentration and shall not in any event exceed One hundred milligrammes per litre in any one sample
 - (viii) carbohydrates in the solution (expressed as glucose) shall not exceed One thousand

milligrammes per litre

(ix) copper nickel zinc tin barium chromium and lead (each expressed as the metal) shall not exceed Twenty milligrammes per litre individually or in total

(x) cadmium and mercury shall not exceed One milligramme per litre individually

(xi) total phenol (as phenol) shall not exceed One hundred milligrammes per litre

(xii) all solvent layers shall be removed

(xiii) the content of free and saline ammonia (expressed as N) shall not exceed One hundred and fifty milligrammes per litre

(xiv) sulphates (expressed as SO_4) shall not exceed One thousand five hundred milligrammes per litre daily average

(b) Without prejudice to the provisions of Clause 9(a) the Effluent shall not contain any substances of a nature or quality likely to injure the Authority's sewers or interfere with the free flow of their contents or to injure the Authority's Treatment Works or any machinery or equipment installed thereat or to interfere with any of the processes of purification

(c) I.C.I. shall maintain at the Works balancing tanks of at least 80,000 gallons capacity for the Effluent and shall maintain the normal flow from the Works within the agreed limits pertaining at the date hereof or such other flow as may be agreed from time to time with the Officer or the Director of Operations for the time being of the Authority

10. I.C.I. will during the currency of this Agreement maintain an inspection chamber at the point marked "C" on the said plan at which samples of the Effluent flowing into the Authority's

sewers can be taken I.C.I. will install and maintain such continuous sampling and flow recording apparatus as may be agreed with the Authority for taking samples in accordance with Appendix 'A' and measuring the volume of the Effluent at the point marked "C" on the said plan. Duly authorised representatives of the Authority shall be entitled at all times and without giving prior notice to inspect the Works and to inspect, examine and test apparatus installed therein in pursuance hereof and to take samples of the Effluent and to consult I.C.I.'s records of the samples volumes and rates of flow of the Effluent

11. I.C.I. agrees with the Authority as follows:-

- (a) Not to discharge into the Authority's sewerage system effluent which at the points marked "A" and "B" on the said plan does not conform to the conditions set out in Clause 9
- (b) To give the Authority any reasonable information about the nature, composition, temperature and volume of the Effluent discharged from the Works from time to time into the Authority's sewers and at as early a time as practicable notice of cessation of discharge

12. SHOULD the flow of Effluent discharged through the sewer shown marked "A" on the said plan regularly exceed Forty-two thousand gallons in any one hour I.C.I. will arrange for the excess of Effluent to be discharged through the sewer shown marked "B" on the said plan and for the purposes of this clause a discharge into the said sewer shown marked "A" in excess of Forty-two thousand gallons in any one hour occurring on average once a week over a ten week period shall be regarded as a regular excess discharge. For the purposes of this clause I.C.I. shall install to the satisfaction of the Authority a connecting sewer between the sewer marked "A" on the said plan and the sewer marked "B" on the said plan within twelve months from the

signing of this Agreement .

13. I.C.I. shall indemnify the Authority against any claims costs charges or other sums to which the Authority may (saving their own negligence or the negligence of one or more of their employees or contractors) become legally liable by reason of any breach by I.C.I. of the limitations as to their Effluent contained in this Agreement or in any subsequent modification hereof

14. IN the event of a breach of any of the conditions contained in this Agreement I.C.I. shall forthwith collaborate with the Authority and their Officers to eliminate the said breach

15. EITHER party may by six months' written notice to the other expiring not earlier than two years from the completion of the extensions as certified by the Authority or from the effective date of the last review (as the case may be) require review of any provisions in the Agreement except those relating to the servicing of capital and reservation of capacity in the Treatment Works for the Effluent

23/1/60 ← (date)
16. ANY variation agreed under Clause 15 shall take effect on the First day of April next following the service of notice and if no agreement is reached the matter shall be referred to arbitration

17. ANY dispute under this Agreement shall be referred to a single agreed arbitrator or in default to a single arbitrator nominated by the President for the time being of the Institute Water Pollution Control such nominee to act as an expert and the proper charges of such nominee shall be in the award of the nominee

A S W I T N E S S the hands of the parties hereto the day and year first before written

APPENDIX 'A'

Trade effluent strength shall be measured by the Total Oxygen Demand (T.O.D.) milligrammes per litre which is defined as the

Chemical Oxygen Demand (C.O.D.) milligrammes per litre plus
(4.57 x Total Nitrogen) milligrammes per litre The C.O.D. shall
be determined by the method set out in the Department of the
Environment Publication 'Analysis of Raw Potable and Waste Waters
1972' with suitable modifications agreed between the Authority
and I.C.I. Suspended solids water immiscible grease and oil
(water immiscible grease and oil as determined by a mutually
agreed method) and other determinations shall be carried out in
accordance with the methods set out in the above publication
Samples of the Effluent shall be taken at Point "C" on the
attached plan and shall be in accordance with the following
programme:-

1. I.C.I. will collect half hourly samples each of
Two hundred mls and using such continuous sampler
as may be agreed in the pursuance of Clause 10
of the Agreement
2. Each day I.C.I. will prepare a bulk sample of
the previous day's Effluent using such proportional
sampler as is agreed with the Authority
3. I.C.I. will determine each day the T.O.D. (as
defined above) and suspended solids content of
the bulk samples by analysis in accordance with
the method contained in the Department of the
Environment Publication Analysis of Raw Potable
and Waste Waters 1972 edition or as may be agreed
otherwise between the parties hereto
4. For the purpose of calculating the quarterly
charge all figures of the daily analysis and
recorded volumes of Effluent discharged to the
sewer shall be forwarded to the Officer at the end
of each month
5. All half-hourly samples collected by the continuous
sampler and the daily average bulk sample will be

retained by I.C.I. for Twenty-four hours after being collected. The Officer or any person authorised by him may at his discretion collect any or all of these samples to enable him to check the analysis provided by I.C.I. Limited. A proportion of all such samples shall be left with I.C.I. for check analysis.

6. The Officer or any person authorised by him may at his discretion take samples manually from the Effluent discharged and analyse these as a further check on the accuracy of both I.C.I. analyses and the continuous sampler. A portion of all such samples will be left with I.C.I. for check analysis.
7. If the analysis of T.O.D. strength or of Suspended Solids content by I.C.I. differ from those of the Officer by more than Five per cent of the latter the parties hereto will immediately carry out the necessary investigations to determine the cause of difference and I.C.I. should such difference reflect upon the efficiency of the continuous sampling will take immediate steps to rectify such deficiency.
8. If the recording or other apparatus ceases to function satisfactorily then the Officer shall be so informed and the Authority reserve the right to make estimates of the volume and composition of the trade Effluent based upon information previously known to the Authority until such time as the said apparatus is operating to the satisfaction of the Authority.

SIGNED by the said
WILLIAM HUGH CRACKLE
in the presence of:-

W. H. Crackle

T. J. Kean
N. W. W. A.
Warrington
Solicitor

SIGNED by the said
MICHAEL JOSEPH O'BRIEN
in the presence of:-

FOR AND ON
IMPERIAL CHEMICAL INDUSTRIES LTD.
PHARMACEUTICALS DIVISION.

Alice Power
Imperial Chemical Industries Ltd.
Pharmaceuticals Division
Manchester
Legal Assistant

M. J. O'Brien
M. J. O'BRIEN
DIRECTOR ASSISTANT SECRETARY

DATED

24th September 197

NORTH WEST WATER AUTHORITY

- and -

L.C.I. LTD.

AGREEMENT

W. H. CRACKLE
Solicitor
North West Water Au
Great Sankey
Varrington

ZENECA

ZENECA Pharmaceuticals

Alderley House
Alderley Park
Macclesfield
Cheshire SK10 4TF
England

Telephone 0625 552323
Telex 669095/669032 ZENPHNL G
Fax- Main 0625 525022/525272
Fax- Department 0625

TO WHOM IT MAY CONCERN

Direct Fax: 0625 585618

Your Ref	Our Ref	Direct Line	Tel ext	Date
	JRM415/mh 58/-	0625 513095	3095	19 October 1994

CERTIFICATE STATEMENT

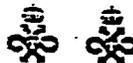
This is to certify that we, ZENECA Limited of Macclesfield, Cheshire, England, being the manufacturers of 'Zoladex' in the UK comply or will comply with all applicable United Kingdom regulations and by-laws governing the emissions resulting from the manufacturing process for the 'Zoladex'.

Yours faithfully
For and on behalf of
ZENECA Limited



Approved as to
legal form by J.R. 111

L Biggins
Assistant Secretary
Zeneca Pharmaceuticals



6.4.4 Effect of Approval on Compliance with Current Limits at the Production Site

The production of "ZOLADEX" will have no impact on compliance with current environmental legislation and permits.

Production of the Zoladex drug product will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations.

6.5 Emission of Substances from Packing Facility

The only emissions from the final packing facility will arise from cleaning operations and the disposal of small amounts of off-specification material and returned product. These emissions will be treated as detailed below.

6.5.1 Aqueous Wastes

All waste water from the site is treated in the New Castle County Municipal Sewer System at the Wilmington Treatment Facility. All discharges meet the relevant permits.

6.5.2 Solid Wastes

Solid wastes are collected and segregated. All wastes which have been in contact with active material are incinerated in an approved facility.

6.5.3 Site Environmental Permits

6.5.4 Permits

Waste Water Permit

Departmental of Public Works of New Castle County Number #WDP-76-025.

Hazardous waste generator permit

United States Environmental Protection Agency.

Number DED0547431909

Air permits

Departmental of Natural Resources and Environmental Resources of the State of Delaware and are as follows:

Permit #	Name
80-0863	Steam Boiler #1
80-0864	Steam Boiler #2
80-0872	Sorbitrate Dust Collector
81-0049	Pilot Plant Granulator
81-1017	Sorbitrate Granulator
82-0961	Nolvadex Dust Collector
82-0962	Nolvadex Granulator
82-0963	Nolvadex Vacuum System
82-0964	Tenormin Vacuum System
82-0965	Tenormin Granulator
82-0966	Tenormin Dust Collector
88-0010	Steam Boiler #3

89-0110	Pilot Plant Dying Oven Exhaust
89-0123	Pilot Plant Coating Pan Exhaust
89-0155	Liquid Manufacturing Dust
Collector	
90-0015	Packaging Dust Collector
91-0596	Pilot Plant Dust Collector

6.5.4 Effect of Approval on Compliance with Current Limits at the Production Site

The packing of the Zoladex drug product will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations.

6.5.5 Effect of Approval on Compliance with Current Limits at the Production Site

The packing of the Zoladex drug product will be controlled so as to ensure the site continues to meet all the relevant Agreements, Authorisations and Permits. There will be a minimal increase in the amount of materials discharged from the site which will be controlled using existing systems. The nature and amounts of these materials is such that they will be accommodated within the terms of the existing permits and authorisations.

6.6 Estimate of Maximum Yearly Market Volume

Confidential

**APPEARS THIS WAY
ON ORIGINAL**

SECTION 7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Both Goserelin Acetate and the Copolymer are rapidly metabolised as described in the new drug application for "Zoladex". The products of the breakdown are largely naturally occurring substances.

The material is rapidly degraded under both aerobic and anaerobic conditions.

**REARS THIS WAY
ON ORIGINAL**

ZENECA

BLS1737/B

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ZOLADEX: Determination of Ready
Biodegradability by OECD test guideline 301F

Brixham
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Freshwater Quarry
Brixham
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The biodegradability of Zoladex (supplied by ZENECA Pharmaceuticals, identified as U9000674 Goserelin acetate (NQ) CPD, Batch ref 257GAP, and received on 12 May 1994) was tested in this laboratory during the period 2 to 30 June 1994.

The substance was tested by the OECD test guideline 301F for ready biodegradability (OECD Guidelines for the Testing of Chemicals, Paris, 1992). In outline this procedure involved stirring concentrations of 100 and 50 mg/l of the test substance in an aqueous medium with 30 mg/l of activated sludge for a period of 28 days. During this 28-day period the biochemical oxygen demand (BOD) was measured, and at the end of the experiment the level of organic carbon remaining in the aqueous phase was also measured. The test was conducted to the specifications of Brixham Environmental Laboratory Standard Operating Procedure BI14 version 13.

Parent compound analysis was performed on the day 0 stock solution, and on the bottle contents on day 28. The HPLC method used was specified in Brixham Environmental Laboratory Standard Operating Procedures AL200 version 03 and AL301 version 01.

The results, expressed on the basis of the ratio of the BOD to the chemical oxygen demand (COD), are summarised in Table 1, together with the corresponding results for sodium acetate, the positive control used in the experiment. The results in Table 2 show the ultimate biodegradation calculated on the basis of the organic carbon remaining in the aqueous phase. Table 3 shows parent compound analytical results.

Results show that Zoladex is readily biodegradable under the test conditions used.

Further details may be obtained from the Brixham Environmental Laboratory by quoting the Study Number AA0379/C.

M. Latham
28 Sept. 94

M Latham
Principal
Investigator
Biodegradation

P A Johnson
23.9.94

P A Johnson
Principal
Investigator
Analysis

D S Morris
28 Sept 1994

D S Morris
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N R Gore
3 October 1994

N R Gore
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CIRCULATION

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ZOLADEX: Determination of anaerobic biodegradability

The anaerobic biodegradability of Zoladex (supplied by ZENECA Pharmaceuticals, identified as U9000674 Goserelin acetate (NQ) CPD, Batch ref 257GAP, and received on 12 May 1994) was tested in this laboratory during the period 28 June to 23 August 1994.

The test procedure was based on that described by ISO Draft Method ISO/CD11734 as specified in the Brixham Environmental Laboratory Standard Operating Procedure B196 version 05.

Test chemical was incubated with digested sludge under anaerobic conditions for a 56 day period. Percentage biodegradation was calculated from the total carbon formed (as gas plus dissolved inorganic carbon) and the known amount of carbon added as test chemical. PEG 400 was used as a reference chemical (>60% biodegradability expected).

Parent compound analysis was performed using an HPLC method defined by Brixham Environmental Laboratory Standard Operating procedures AL200, version 03 and AL301, version 01. The stock solution was analysed on day 0, as well as representative test bottles: blank control, test bottle and an abiotic control bottle containing Zoladex at the test concentration but without anaerobic digested sludge. Representative test bottles were analysed at the end of the study. Abiotic control bottles provided a check for anaerobic bioelimination.

A degree of anaerobic biodegradability was exhibited by Zoladex over the test period and the parent compound analytical results show that Zoladex was totally bioeliminated under the test conditions. The mean level of biodegradability of the reference material (63%) showed the digested sludge to be active. The summarised biodegradation results are given in Table 1 and the parent compound analytical results are given in Table 2.

Further details may be obtained from the Brixham Environmental Laboratory by quoting the study number AA0379/B.

M. Latham
28 Sept 1994

M Latham
Principal
Investigator
Biodegradation

Peter Johnson
28.9.94.

P A Johnson
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Analysis

D S Morris
28 Sept 1994

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3 October 1994

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Manager

CIRCULATION

Copy number

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2 (unbound)
3
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ZENECA Pharmaceuticals, Alderley Park
Brixham Environmental Laboratory
Brixham Environmental Laboratory

Brixham Environmental Laboratory
The UK office of ZENECA Limited
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APPENDIX 1

CALCULATION AND EXPRESSION OF RESULTS

Calculation of gas production

For each vessel, the total gasified carbon, C_T (mg), is given by:

$$C_T = (C_H + C_L) \text{ mg}$$

where C_H = carbon in the headspace (mg), and
and C_L = inorganic carbon in the liquid phase (mg),
ignoring the relatively small amount of methane in solution.

The number of moles of C-containing gas in each vessel is calculated from the gas laws assuming ideal behaviour, thus:

$$n = \frac{dP \cdot V_H}{RT}$$

where n = g-moles of gas
 dP = pressure difference between initial and final readings (atm.) (When intermediate measurements are made and excess gas is released to the atmosphere, the individual pressure differences are added together to give the total increase in pressure. No release to atmosphere is performed when negative pressure readings are observed).

V_H = headspace volume (litres i.e. 0.06)
 T = temperature ($^{\circ}$ Kelvin i.e. 308)
and R = the gas constant (0.08205 litres atm moles $^{-1}$ degree $^{-1}$)

Since 1 g-mole of CH_4 and 1 g-mole of CO_2 each contain 12g C, the headspace C is given by

$$C_H = (12 \times n \times 10^3) \text{ mg}$$

The inorganic carbon in the liquid phase is given by

$$C_L = (\text{DIC} \times V_L) \text{ mg}$$

where V_L = volume of digesting liquor (litres i.e. 0.1)
and DIC = concentration of dissolved inorganic carbon in the liquor (mg/litre)

$$\text{Thus } C_T = (12 \times n \times 10^3) + (\text{DIC} \times V_L) \text{ mg.}$$

Extent of biodegradation

The percentage biodegradation is given by:

$$\% \text{ biodegradation} = \frac{C_{T(\text{control})} - C_{T(\text{test})}}{\text{test chemical added (mg C)}} \times 100$$

where $C_{T(\text{test})}$ = total gasified carbon, mean of replicates for test chemical (mg)
and $C_{T(\text{control})}$ = total gasified carbon, mean of replicates for controls (mg)

SECTION 8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

The materials which are finally released to the environment are largely naturally occurring. As they are released in small quantities there will be no significant environmental effect from the production and use of "Zoladex". Goserelin acetate is manufactured in quantities not expected to exceed 20kg per year. As a result the amount of waste to be treated by the appropriate emission control devices is also very low. State of the art waste water treatment processes and waste incineration procedures are used in the goserelin acetate manufacturing process. It is unlikely to have any significant effect on the environment. No adverse effects can reasonably be anticipated from substances produced as a result of the proposed use of goserelin acetate.

SECTION 10. MITIGATION MEASURES

The measures for controlling emissions from the manufacturing process are described in section 6

10.1 Emergency and Spillage Procedures

There is an emergency plan covering all aspects of the sites' activities. Plans are in place to contain and remove any spillages or other loss of containment. The manufacture of Zoladex will be covered by these arrangements.

10.2 Control of Workplace Exposure

10.2.1 Control Procedures

Primary control is by containment within the manufacturing plants. This is supplemented, where appropriate, by local exhaust ventilation. Where necessary personal protective equipment is used to prevent workplace exposure.

10.2.2 Monitoring

Monitoring programmes are in place to ensure that the controls remain effective. These programmes include monitoring both the performance of equipment and sampling the atmosphere in the workplace.

10.2.3 Information and Training

Safety Data Sheets are available for all materials used in the manufacture of ZOLADEX

All operators are fully trained to understand the hazards of the materials and the procedures in place to prevent emissions to the environment.

10.3 Waste Minimisation

ZENECA Pharmaceuticals has a policy of minimising waste and developing routes of manufacture which have the minimum impact to the environment. The Company's management have programmes in place to ensure these policies are progressed.

SECTION 11. ALTERNATIVES TO PROPOSED ACTION

There are no alternatives to the proposed action.

The actions taken in controlling emissions and disposing of waste materials will ensure that there are no adverse effects on the environment.

However not approving this application could jeopardise the supply of the beneficial drug product Zoladex in the United States. Given the absence of any significant environmental impact that would result from the proposed manufacture and use of goserelin acetate is environmentally safe in every respect.

12. PREPARERS

ment was prepared by Martin Rackham, Occupational Hygiene and Environmental Affairs
of ZENECA PHARMACEUTICALS. He has a Bachelors Degree in Chemistry and
and a Masters Degree in Occupational Hygiene.

SECTION THIRTEEN

SECTION 13. CERTIFICATION

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



Martin Rackham MSc BSc MIOH
Occupational Hygiene and Environmental Affairs Manager
International Safety, Health and Environment Department
ZENECA Pharmaceuticals

REFERENCES

As necessary by the agency the applicant will provide additional appropriate references.

SECTION 15 APPENDICES

Safety Data Sheet

SAFETY DATA SHEET**1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION**

Name: GOSERELIN ACETATE

Alternative Names

ICI 118,630

Zoladex

3-(5-Oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-(3-O-tert-butyl)-D-seryl-L-leucyl-L-arginyl-L-prolyl)carbazamide acetate

2. COMPOSITION/INFORMATION ON INGREDIENTS

CAS No. : 145781-92-6
EEC No. : None assigned
Use : tumour inhibitor

HAZARDOUS INGREDIENT(S)	CAS No.	Symbol	R Phrases
Goserelin acetate	145781-92-6	T	R60

3. HAZARDS IDENTIFICATION

May cause reproductive effects in males and females.
May impair fertility.

Health Hazard Category : A

4. FIRST-AID MEASURES

Inhalation : Remove patient from exposure, keep warm and at rest.
Obtain medical attention.
Skin Contact : Remove contaminated clothing. Wash skin with water.
Eye Contact : Irrigate with eyewash solution or clean water, holding the eyelids apart, for at least 10 minutes. Obtain medical attention.
Ingestion : Wash out mouth with water. Obtain medical attention.

Further Medical TreatmentSymptomatic treatment and supportive therapy as indicated.

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ZENECA LIMITED PH507/6
(Page: 1-continued)

SAFETY DATA SHEET

Name: GOSERELIN ACETATE

5. FIRE-FIGHTING MEASURES

Combustible.

Extinguishing Media : water spray, foam, dry powder or CO2.

6. ACCIDENTAL RELEASE MEASURES

Ensure suitable personal protection (including respiratory protection) during removal of spillages.
Moisten spillages with water. Wash the spillage area with water.

7. HANDLING AND STORAGE

7.1 HANDLING

Do not breathe dust. Avoid contact with skin and eyes.
Atmospheric levels should be controlled in compliance with the occupational exposure limit.

Avoid exposure. Obtain special instructions before use. Female employees should be restricted from areas where exposure above the OEL for short periods is likely.

7.2 STORAGE

Keep container tightly closed. Protect from light. Keep away from moisture.

Storage Life : 2 year(s)

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Wear suitable respiratory protective equipment if exposure to levels above the occupational exposure limit is likely.
Wear suitable protective clothing.

Occupational Exposure Limits

HAZARDOUS INGREDIENT(S)	LTEL 8hr TWA		STEL		
	ppm	mg/m ³	ppm	mg/m ³	
Goserelin Acetate	-	0.0025	-	-	COM

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(UK00 Date: 0895)

ZENECA LIMITED PH507/6
(Page: 2-continued)

SAFETY DATA SHEETName: **GOSERELIN ACETATE**

9. PHYSICAL AND CHEMICAL PROPERTIES

Form : powder
Colour : white to almost white
pH (Value) : No data.
Melting Point (Deg C) : decomposes on heating
Flash Point (Deg C) : Not applicable.
Flammable Limits : Not applicable.
Auto Ignition Temperature (Deg C) : No data.
Vapour Pressure (mm Hg) : No data.
Solubility (Water) : soluble
Solubility (Other) : soluble in: DMSO and DMF
practically insoluble in: acetone
chloroform ether
Specific Gravity : No data.
Vapour Density (Air= 1) : No data.
Dissociation constant: 6.2

10. STABILITY AND REACTIVITY

Hazardous Reactions : None known.
Hazardous Decomposition Product(s) : None known.

11. TOXICOLOGICAL INFORMATION

Inhalation : High atmospheric concentrations in excess of the occupational exposure limit may lead to similar effects in women as those described under long term.
Skin Contact : Unlikely to be hazardous by skin absorption. No evidence of irritant effects from normal handling and use.
Eye Contact : No evidence of irritant effects from normal handling and use.
Ingestion : May cause adverse effects as described under long term.
Long Term Exposure : May cause reproductive effects in males and females. May impair fertility. Repeated exposure to levels well above the occupational exposure limit produces adverse effects

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ZENECA LIMITED PH507/6
(Page: 3-continued)

SAFETY DATA SHEET

Name: GOSERELIN ACETATE

on the menstrual cycle in women causing suppression of ovulation and hot flushes, and in men a reduction in fertility and suppression of libido. These effects are reversible after cessation of dosing. None of these effects are likely to occur in humans, provided exposure is maintained at or below the occupational exposure limit.

12. ECOLOGICAL INFORMATION

Toxicity

No information available.

13. DISPOSAL CONSIDERATIONS

Disposal should be in accordance with local, state or national legislation.

14. TRANSPORT INFORMATION

Not Classified as Dangerous for Transport.

15. REGULATORY INFORMATION

Users should ensure that they comply with any relevant local, state or national legislation.

EEC Classification : TOXIC

Hazard Symbol : T
Risk Phrases : R60: May impair fertility.
Safety Phrases : S53: Avoid exposure. Obtain special instructions before use.
S22: Do not breathe dust.
S36: Wear suitable protective clothing.

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ZENECA LIMITED PH507/6
(Page: 4-continued)

SAFETY DATA SHEET

Name: GOSERELIN ACETATE

16. OTHER INFORMATION

This data sheet was prepared in accordance with Directive 91/155/EEC (93/112/EC).

The following sections contain revisions or new statements: 2,3,7,11,15

GLOSSARY

OES : Occupational Exposure Standard (UK HSE EH40)
MEL : Maximum Exposure Limit (UK HSE EH40)
COM : The company aims to control exposure in its workplace to this limit
TLV : The company aims to control exposure in its workplace to the ACGIH limit
TLV-C: The company aims to control exposure in its workplace to the ACGIH Ceiling limit
MAK : The company aims to control exposure in its workplace to the German limit
Sk : Can be absorbed through skin
Sen : Capable of causing respiratory sensitisation

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(UK00 Date: 0895)

ZENECA LIMITED PH507/6
(Page: 5-Last Page)

SAFETY DATA SHEET**1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION**

Name: LACTIDE/GLYCOLIDE COPOLYMER (50:50)

Alternative Names

Lactic/Glycolic acid copolymer
Zoladex copolymer

2. COMPOSITION/INFORMATION ON INGREDIENTS

CAS No. : None assigned
EEC No. : None assigned
Use : excipient

HAZARDOUS INGREDIENT(S)	CAS No.	Symbol	R Phrases
-------------------------	---------	--------	-----------

Contains no Hazardous Ingredients 91/155/EEC (93/112/EC)

3. HAZARDS IDENTIFICATION

Unlikely to cause harmful effects under normal conditions of handling and use.

Health Hazard Category : D

4. FIRST-AID MEASURES

Inhalation : Remove patient from exposure.
Skin Contact : Remove contaminated clothing. Wash skin with soap and water.
Eye Contact : Irrigate with eyewash solution or clean water, holding the eyelids apart, for at least 10 minutes. Obtain medical attention.
Ingestion : Wash out mouth with water. Obtain medical attention if ill effects occur.

Further Medical Treatment

Symptomatic treatment and supportive therapy as indicated.

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(UK00 Date: 0895)

ZENECA LIMITED PH508/3
(Page: 1-continued)

SAFETY DATA SHEET

Name: LACTIDE/GLYCOLIDE COPOLYMER (50:50)

5. FIRE-FIGHTING MEASURES

Combustible. Burns with flames.

Extinguishing Media : water spray, foam, dry powder or CO2.

6. ACCIDENTAL RELEASE MEASURES

Clear up spillages. Wash the spillage area with water. Transfer to a container for disposal.

7. HANDLING AND STORAGE

7.1 HANDLING

Do not breathe dust. Use extraction and ventilation arrangements.

7.2 STORAGE

Keep container tightly closed.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Wear gloves, eye protection and an approved dust mask if dust is generated during handling.

Occupational Exposure Limits

HAZARDOUS INGREDIENT(S)	LTEL 8hr TWA		STEL	
	ppm	mg/m3	ppm	mg/m3

No Occupational Exposure Limit Assigned

9. PHYSICAL AND CHEMICAL PROPERTIES

Form	: crystalline powder
Colour	: white / pale brown
Minimum Ignition Energy (mJ)	: >100

(Revision: 03 Date: 0895)
(UK00 Date: 0895)

ZENECA LIMITED PH508/3
(Page: 2-continued)

SAFETY DATA SHEET

Name: LACTIDE/GLYCOLIDE COPOLYMER (50:50)

10. STABILITY AND REACTIVITY

Hazardous Reactions : No information available.

11. TOXICOLOGICAL INFORMATION

Inhalation : Unlikely to be hazardous by inhalation.

Skin Contact : No evidence of irritant effects from normal handling and use.

Eye Contact : No evidence of irritant effects from normal handling and use.

Ingestion : Unlikely to be hazardous if swallowed.

Long Term Exposure : No information available.

12. ECOLOGICAL INFORMATION

Toxicity
No information available.

13. DISPOSAL CONSIDERATIONS

Disposal should be in accordance with local, state or national legislation.

14. TRANSPORT INFORMATION

Not Classified as Dangerous for Transport.

(Revision: 03 Date: 0895)
(UK00 Date: 0895)

ZENECA LIMITED PH508/3
(Page: 3-continued)

SAFETY DATA SHEET

Name: LACTIDE/GLYCOLIDE COPOLYMER (50:50)

15. REGULATORY INFORMATION

Not Classified as Dangerous for Supply/Use.

Users should ensure that they comply with any relevant local, state or national legislation.

16. OTHER INFORMATION

This data sheet was prepared in accordance with Directive 91/155/EEC (93/112/EC).

The following sections contain revisions or new statements: 1,5,9

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(UK00 Date: 0895)

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(Page: 4-Last Page)