CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-521

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Infasurf™
(Calf Lung Surfactant Extract)
(no USAN name assigned)
Sterile Suspension

NDA 20-521

Ony Inc.

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF PULMONARY DRUG PRODUCTS
(HFD-570)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-521

Infasurf™

(No USAN Name assigned)

Sterile Suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal Agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Infasurf™, Ony Inc. has prepared an environmental assessment (attached) in accordance with [21 CFR 25.31a(a), which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. The maximum expected environmental concentration is at a level that normally relieves the applicant from completing format items 7, 8, 9, 10, 11, and 15 in accordance with the Tier 0 approach specified in the *Guidance for Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements*.

Infasurf™ is a natural pulmonary surfactant obtained by extraction of porcine lung tissue. It is administered as a sterile suspension intratracheally in the treatment of neonatal respiratory distress syndrome (RDS) . Both the drug substance and drug product will be manufactured by Ony Inc., Baird Research Park, New York University at Buffalo, Amherst, New York. The finished drug product will be used primarily in hospitals and clinics where premature infants are treated.

Infasurf™ may enter the environment from excretion by patients, from disposal of pharmaceutical waste and from emissions from manufacturing sites.

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. 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.

/S/

2/6/97
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

/S/

2/16/97
Date

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

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

Copies:

HFD-570

Betty Kuzmik, CSO/PM
Original to NDA 20-521, through Betty Kuzmik, CSO/PM
Division File for NDA 20-521

HFD-205

FOI Copy

HFD-357

EA File for NDA 20-521
Docket File
C. Berninger

APPEARS THIS WAY
ON ORIGINAL

FOI EA
NDA 20-521

1.0 DATE

Original Submission: August 1995

Amended Submission: October 1996

2.0 NAME OF APPLICANT/PETITIONER

ONY Inc.

3.0 ADDRESS

Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Town: Amherst

County: Erie

State: New York

Contact Person: William Ferguson
Director of Operations
(716)636-9096

4.0 DESCRIPTION OF PROPOSED ACTION

The intent of this report is to provide sufficient information as specified in the Codes of Federal Regulations, Food and Drugs, 21 CFR Part 25.31 and consistent with 40 CFR Part 1500.4(J) and 1502.21.

4.1 REQUESTED APPROVAL

Infasurf®, a human drug product, is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal administration only. Infasurf® has been researched and clinically tested for several years for both the prevention (prophylaxis) and the treatment (rescue) of neonatal respiratory distress. ONY Inc. is requesting the approval to manufacture, package, and distribute Infasurf® out of their facility in Amherst, New York.

4.2 NEED FOR THE ACTION

Prevention studies include premature infants less than 33 weeks gestation and treatment studies include all premature infants with established respiratory distress syndrome, RDS, (confirmed by clinical and radiologic findings) requiring mechanical ventilation. Infasurf® (calf lung surfactant extract), when instilled intratracheally into the lungs of premature, surfactant deficient infants before or near the onset of breathing reduces the incidence and severity of respiratory distress syndrome and improves lung function.

The estimated number of pediatric cases, who would annually benefit from Infasurf®, are 100,000 - 120,000 throughout the United States. There is no higher use of surfactant associated with geographical locations. At the successful completion of the clinical trial period, submission of a New Drug Application will be filed with this Confidential Environmental Assessment. ONY Inc. is the developer of Infasurf®, and is proposing its production at the existing facility where the product was developed. It is requested that approval be given, by the FDA, for the use of this drug in an environmentally sound, economically reasonable, and socially acceptable manner.

4.3 LOCATION WHERE THE PRODUCTS WILL BE PRODUCED

The production facility, ONY Inc., for Infasurf® is located at Baird Research Park, of New York State University at Buffalo, Town of Amherst, Erie County, New York.

4.4 LOCATION WHERE THE PRODUCTS WILL BE USED AND DISPOSED OF

The finished product will be used throughout the United States and is not limited to a certain geographical region of the country. However, the ultimate use of the product will be in hospitals for the prevention (prophylaxis) and the treatment (rescue) of neonatal respiratory distress.

This substance has been researched and clinically tested for several years. A review of the study performed as part of a clinical trial period indicated that the amount of waste expected to enter the environment was minimal and, due to its non-toxic characteristics, was not considered a threat to the environment.

Disposal of the product may be needed due to manufacturing activities in the form of discarded out of specification lots, from the discarding of returned and rejected goods or from end users. The physical and chemical characteristics of Infasurf® does not require a controlled method of disposal of the waste generated. Therefore, upon the need for disposal or termination of the drug, or individual unit of empty or partially empty finished product, the liquid residue, which is supplied in glass vials, can be discharged into a sink which is connected to a sanitary sewer. The glass vial may then be discarded into a secured container to maximize the safety related to glass handling, and treated in a similar manner as regular solid waste.

4.5 TYPES OF ENVIRONMENTS PRESENT AT AND ADJACENT TO PRODUCTION LOCATIONS

Baird Research Park is located in an industrially zoned district, with the surrounding area being relatively flat and the climate cold and snowy in the winter and moderately warm in the summer. Current facilities located at the Park consist of various research and development laboratories, commercial and industrial oriented services. Synthesis of the chemical and its incorporation into the product will take place at the only existing designated facility of ONY Inc. located at Baird Research Park, 1576 Sweet Home Road, Amherst, New York.

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

Infasurf® is a sterile, non-pyrogenic pulmonary surfactant. It is an organic solvent extract of calf lung suspended in 0.9% saline for irrigation. This pharmaceutical compound is formulated in the production section of ONY, after having been thoroughly researched by the Research and Development (R&D) section.

The raw materials used in the manufacturing of this drug product in the production facility, includes the calf lung, the whole lung surfactant suspension 0.9% saline of the organ, 0.9% sodium chloride USP, sterile water for irrigation, USP,

The following section provides a description of the materials used in the formulation of the drug substance (calf lung surfactant extract - CLSE) and drug product (Infasurf®).

5.1 NOMENCLATURE

Chemical Name:	Sodium Chloride
CAS Reg. #:	7647-14-5
Molecular Weight:	58.44
Molecular Formula:	NaCl
Physical Phase:	Granular
Additives:	Purified Water, USP
Impurities:	None

Chemical Name:	
CAS Reg. #:	
Molecular Weight:	
Molecular Formula:	
Physical Phase:	
Additives:	
Impurities:	

Chemical Name:
CAS Reg. #:
Molecular Weight:
Molecular Formula:
Physical Phase:
Additives:
Impurities:

Chemical Name:
CAS Reg. #:
Molecular Weight:
Structural Formula:
Physical Phase:
Additives:
Impurities:

Additional Chemicals: 0.9% Sodium Chloride USP
Sterile Water for irrigation, USP

CLSE (Drug Substance) is made from calf lung, purified water, sodium chloride granular, USP, 0.9% sodium chloride USP, and sterile water USP. CLSE is the lipid and protein moieties of natural lung surfactant dissolved in . This complex biologic material is 90-95% phospholipid, and 1-3% hydrophobic surfactant specific proteins (SP-B, SP-C). The presence and quantification of other possible trace (<1%) neutral lipid materials in CLSE is not available.

Infasurf® contains CLSE, 0.9% sodium chloride irrigation, USP, sterile water USP, and trace amounts (≤ 10 ppm) of and (≤ 200 ppm) Information concerning the molecular weight and structural formula for calf lung surfactant extract is unknown as it is a complex biologic material. Therefore, the previous format used for the identification of the chemical substances can not be used in the identification of the aforementioned components.

Note: Appendix A contains confidential information concerning the composition of Infasurf®.

Appendix B contains the Material Safety Data Sheet (MSDS).

6.0 INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The central question in an assessment of environmental impact is: What effects will the proposed action have on the environment of the area affected by the action? More important, are any of these predicted effects adverse, or could they be cause for concern? (Usually, the term environmental impact is reserved for those effects considered significant, especially when they are undesirable or potentially adverse, or those that call for a mitigation or intervention of some kind.)

This section addresses the questions and concerns raised by the introduction of substance into the environment. Its scope is the result of several influences: United States Environmental Protection Agency (USEPA), New York State Department of Environmental Conservation (NYSDEC) regulations and recommendations, local agencies, research findings, and the experience of consultants, with similar projects.

The basis for organizing the study and for presenting the results is a list of environmental issues or "parameters" judged relevant to the current project. A convenient way to classify these issues is in three broad categories: effects on the physical environment; effects on the biological environment; and effects on the socio-economic environment.

RESEARCH & DEVELOPMENT

The Research & Development section of ONY Inc., uses a large number of chemicals in small quantities. The materials in use at any given time will vary depending upon the focus of the Research & Development program. such as and are commonly used for extraction and analysis. is the most widely used acid.

Research and development in the pharmaceutical industry encompasses several fields, including chemical, microbiological, and pharmacological research.

The R&D section is divided into two groups, the Synthetic Chemistry Division and the Product Development Division.

PRODUCTION

Infasurf® is produced in batches where the raw materials are used to extract the drug substance from a biological organ. This pharmaceutical compound is

formulated in the production section of ONY, after having been thoroughly researched by the Research and Development (R&D) section. The finished products are sampled and analyzed by ONY (in house) and independent (outside contractor) laboratories. The analysis results are then provided to a QA group for final review and authorization for use. As a result of this stringent implementation of QA/QC programs, during the formulation stage the possibility of reject products has been minimized (three lots since 1987).

PACKAGING

After satisfactory analysis results have been obtained, the formulated compounds are released for packaging into the finished product containers where they are again sampled by QA/QC personnel. To date, there has not been any rejected product during the packaging operation.

6.1 & 6.2 LIST OF SUBSTANCES EXPECTED TO BE EMITTED AND CONTROL EQUIPMENT EXERCISED

The ONY Inc. manufacturing facility is constructed and designed to operate in full compliance with current standards and FDA's good laboratory and manufacturing practices.

The principal waste streams generated by the R&D section are spent solvent, spent corrosive, and expired products. The Production section mostly includes equipment and floor cleaning water and rejected products, and the packaging section consists mostly of shipping containers, paper products, and rejected products.

AIR EMISSIONS AND CONTROL EQUIPMENT

The substances released into the atmosphere as a result of the proposed action includes solvents used for extraction processes, primarily Although the air emissions are minimal, and control equipment is not required, for good pharmaceutical practice, an exhaust laboratory fume hood has been employed. The released chemicals are emitted through the stack of the laboratory fume hood which is equipped with an exhaust blower. This practice is in full compliance with occupational health provision, safety and environmental control regulations of OSHA.

The heating, ventilation, and air-conditioning system is monitored and controlled. The air quality within the facility is maintained by high efficiency particulate absorption (HEPA) filtration. The HEPA filters are protected by pre-filters and

particle counts and velocity are monitored to ensure effectiveness.

LIQUID WASTE STREAM AND CONTROL EQUIPMENT

The liquid waste stream is divided into two categories as follows:

a. Regulated liquid waste and control equipment
b. Non-regulated liquid waste and control equipment

a. REGULATED LIQUID WASTE AND CONTROL EQUIPMENT

The principal waste streams generated at the site include spent solvents, such as used for product processing and recovery. After use, they will be collected in waste storage containers, properly labeled and handled as instructed by the USEPA, and NYSDEC. These containers are stored in an area designated for hazardous waste material storage until it is transported by an USEPA and NYSDEC certified hauler and disposed of in a disposal site which is approved by USEPA and NYSDEC.

b. NON-REGULATED LIQUID WASTE AND CONTROL EQUIPMENT

The liquid waste released due to the proposed action will have low to medium biochemical oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS) and total dissolved solids (TDS) concentration, and are classified as water soluble and non-hazardous material. Physical and chemical characteristics of the drug product does not restrict its discharge into the waste water treatment plant as it is a non-hazardous biologic (municipal sanitary sewer). The final concentration reaching the sewer or the aquatic environment would be undetectable and insignificant. Sanitary waste from toilets, sinks, and non process areas are also discharged directly into the sanitary sewer. All other processes within the building are monitored and discharged into an on-site acid neutralization tank for pH balance. The neutralization tank will then adjust the pH and discharge the waste into a holding tank prior to final discharge to the municipal sanitary sewer.

SOLID WASTE AND CONTROL EQUIPMENT

The non-hazardous solid waste generated at the site includes calf lung, glass vials, laboratory waste and ordinary office and sanitary waste, which will be removed and carted to the landfill. Empty vials and shipping containers generated at the medical facilities where the product is used will be discarded in accordance with local disposal codes and regulations. Since the waste is not considered to be hazardous it will be deposited into designated trash bins for proper disposal. Disposal of production and used debris will be controlled by applicable solid waste regulations imposed at the disposal site.

6.3 CITATION OF AND STATEMENT OF COMPLIANCE WITH APPLICABLE EMISSIONS LEVEL

a. AIR EMISSIONS

Under section 114 of the Act (42 U.S.C.7414), U.S. Environmental Protection Agency has been given the broad authority to evaluate the compliance status of emissions released by any source of pollutant. Subsequent to this Act, NYSDEC has been designated as the regulatory representative of the USEPA.

A recent evaluation of the released material was performed and reported to NYSDEC for an Air Pollution Process Permit. The results indicated that the emitted substances are far below the emission standards and incompliance with the Clean Air Act regulations of NYSDEC, 6NYCRR Part 212.

b. REGULATED WASTE

A permit application for Notification of Regulated Waste Activity has been filed with and approved by the USEPA indicating compliance with Section 3010 of the Resource Conservation and Recovery Act (RCRA), found in the Codes of Federal Regulations (CFR) Title 40, Part 261, Hazardous Waste Regulations.

c. LIQUID WASTE

The amount of waste water released to the sanitary sewer at the production site, due to the proposed action, will not require a discharge permit from the Amherst Metropolitan Sewer District. However, as per the requirements of 40 CFR Part 403.8, for Publicly Owned

Treatment Works (POTW), spot sampling and a review of the operational processes will be performed during the fiscal year by authorities of the sewer district to assure compliance, and/or inform the facility operator of the favorable nutrient for the central treatment facility. A recent sampling of the released material was performed by the Amherst Metropolitan Sewer District through and their investigation indicated compliance and an acceptable operation.

d. NON-REGULATED WASTE

As per NYSDEC Division of Hazardous Waste Material, the fresh calf lung with 0.9% NaCl is not considered a regulated waste, and it does not require any environmental permit, special attention and/or handling. However, all solid disposal methods are conducted in accordance with the solid waste disposal regulations of the State of New York, Erie County.

6.4 THE EFFECT OF THE APPROVAL OF THE PROPOSED ACTION WILL HAVE UPON COMPLIANCE WITH CURRENT EMISSIONS REQUIREMENTS AT THE PRODUCTION SITE

ONY Inc. is designed to meet all applicable emission requirements. No affect of the proposed action is anticipated for continued compliance with current emission requirements.

AIR EMISSIONS

The approval of the proposed action will not have a significant environmental effect at the production site as documented in the NYSDEC permit application.

NON-REGULATED LIQUID WASTE

A commercial/industrial survey conducted by pretreatment Department of the Town of Amherst Sewer System, revealed that, ONY Inc. is in compliance with General Pretreatment Regulations (40 CFR 403.8 (f) (2) (i)) and is not subject to a any restriction or permit for said operation.

SOLID WASTE

Solid waste generated as a result of ONY Inc. operation at the production site is minimal and has no significant environmental effects.

6.5 QUANTITIES AND CONCENTRATIONS OF SUBSTANCES EXPECTED TO ENTER THE ENVIRONMENT

AIR EMISSIONS

In accordance with the Rules of the New York State Department of Environmental Conservation, a permit application was submitted for Process Exhaust and/or Ventilation Systems. Through material-balance calculations it was demonstrated that the processes within this facility are in compliance with all applicable emission standards.

AIR EMISSIONS CALCULATION

(CAS # ;
used per year = 211 gal/yr
80% of the will be captured and discharged into the waste drum for proper disposal.
Emitted = (211 gal/yr) x 1.49 x (8.34 lbs/gal) x 20% Emission Factor = 524.4 lbs/yr

(CAS #
used per year = 213 gal/yr
Emitted = (213 gal/yr) x 0.79 x (8.34 lbs/gal) x 10% Emission Factor = 140.3 lbs/yr

Misc. organic solvents (CAS # NY990-00-0);
Misc. organic solvent used = 3.5 gal/yr
Misc. organic solvent emitted = (3.5 gal/yr) x 0.78 x (8.34 lbs/yr) x 20% Emission factor = 4.55 lbs/yr

Misc. in-organic solvents (CAS # NY999-00-4);
Misc. in-organic solvent used = 2.5 gal/yr
Misc. in-organic solvent emitted = (2.5 gal/yr) x 0.78 x (8.34 lbs/yr) x 20% Emission factor = 3.25 lbs/yr

NON-REGULATED LIQUID WASTE

The waste water discharge into the sewer system from ONY Inc. is expected to be 800 gallons per day (gpd) from the production facility.

REGULATED WASTE

Total regulated waste (hazardous waste) generated at ONY Inc. is estimated to be 5 - 6 gpd.

Note: This is a maximum amount based on full production 4 days/week

SOLID WASTE

Combined solid waste from production, laboratories, office trash and corrugated containers are expected to be 8 cubic yards per week (320 yards per year).

NON-REGULATED LIQUID WASTE

Following the commercial/industrial survey conducted by the Pretreatment Department of the Town of Amherst Sewer System, a sample of the waste water was collected by the town officials and analyzed. The results of the analysis indicated that ONY Inc. is in compliance with the General Pretreatment Regulations (40 CFR 403.8 (f) (2) (i)) and is not subject to any restrictions or permitting for said operation.

EXPECTED INTRODUCTION CONCENTRATION

The drug substance entering the environment as a result of use and disposal, has been estimated based on total fifth year production forecasts. If the following Expected Introduction Concentration (EIC) calculation is less than 1 ppb, it is unlikely to have a significant effect on the environment. (See Confidential Appendix A for EIC calculations).

Since the EIC was calculated to be 4.8×10^{-4} ppb it is unlikely to have a significant effect on the environment. Therefore, Tier 0 has been met. Appendix A contains confidential information concerning the production estimates of Infasurf® and calculation of the EIC.

09 020

12.0 LIST OF PREPARERS

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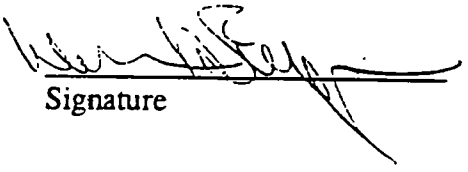
13.0 CERTIFICATION

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

William H. Ferguson
Print Name

Director of Operations
Title



Signature

10-26-96
Date

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Forest Laboratories, Inc.

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United States Environmental Protection Agency, Office of Air Quality Planning and Standards

United States Environmental Protection Agency, Air & Waste Management Division, Hazardous & Solid Waste Program Branch

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- a preliminary appraisal, New York Water.