CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-582

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Follistim

(Follitropin beta for injection)

NDA 20-582

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF METABOLISM and ENDOCRINE

DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-582
Follistim (Follitropin beta for injection]

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

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

In support of their New Drug Application for Follistim (Follitropin alpha for injection, originally called ORG 32489 for injection), Organon prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(5) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product that occurs naturally in the environment. Follitropin beta is a glycoprotein hormone produced by humans(female).

Follitropin beta for injection is a drug manufactured by recombinant DNA technology which is administered as an injection after reconstitution with 0.45% sodium chloride injection in the treatment of female infertility.

The drug substance, Follitropin beta (ORG 32489), is manufactured by

The drug product is manufactured by Organon Inc., 375 Mount Pleasant Avenue, West Orange, New Jersey 07052. The finished drug product will be used by physicians in hospitals, clinics and medical offices. The product will be injected by medical personnel or may be dispensed to patients by prescription.

Follitropin beta(ORG 32489) drug substance may enter the environment through the urine and bile of the user. However, the concentration of these components released into the environment will displace already existing concentrations released from the currently marketed drug product. Also, the concentration will be further diminished when combined with other water-carried wastes which enter the public sewerage and/or waste water treatment systems. It is anticipated that the release of follitropin beta at the levels associated with its production and use will have no adverse effects on the environment.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Waste drug substance and drug product will be disposed of at a licensed landfill facility. At U.S.

hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures.

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.

3/18/97
DATE

PREPARED
Duu-Gong Wu, Ph.D.
Team Leader II
Division of New Drug Chemistry II
Center for Drug Evaluation and Research

3/24/97
DATE

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

Attachment: Environmental Assessment

c.c. Original NDA 20-582
HFD-580/Division file
HFD-580/MJ Rhee/L Pauls
HFD-510/DG Wu
HFD-004/FONSI File NDA #20-582
HFD-004/Docket File
HFD-019/FOI COPY

Project: ORG 32489
Document No.: PDR-369

ORGANON INC.
West Orange, New Jersey 07052

ENVIRONMENTAL IMPACT ASSESSMENT REPORT FOR ORG 32489 FOR INJECTION

Pharmaceutical Development Department
Product Development and Government Affairs
September 14, 1995

ENVIRONMENTAL IMPACT ASSESSMENT REPORT FOR ORG 32489 FOR INJECTION

Table of Contents

ENVIRONMENTAL IMPACT ASSESSMENT REPORT FOR ORG 32489 FOR INJECTION

Table of Contents (continued)

1. **Date:** September 14, 1995

2. **Name of Applicant:** Organon Inc.

3. **Address:** 375 Mount Pleasant Avenue
West Orange, New Jersey 07052

4. **Description of Proposed Action:**

A. Requested Approval

Organon Inc. has filed a new drug application, NDA No. 20-582, pursuant to Section 505 (b) of the Food, Drug, and Cosmetic Act requesting approval to manufacture, package, distribute and sell its two dosage strengths of ORG 32489 for Injection. Each vial of ORG 32489 for Injection contains either 75 International Units (IU) of follicle stimulating hormone (FSH) activity or 150 IU FSH activity. It is supplied as a sterile, lyophilized cake to be reconstituted at time of use with 1 mL of Sodium Chloride Injection 0.45%, which is supplied in the package. This Environmental Impact Assessment Report is being submitted in accordance with 21 CFR 25.31 (a) (b) in abbreviated format, for a substance that occurs naturally in the environment, as directed in item (5) of the previously cited code.

B. Need for Action

Approval of this application will offer women in the United States an alternative, effective and reliable treatment for infertility.

i. Clinical Pharmacology

ORG 32489 for Injection is similar to Metrodin®, urofollitropin (Serono), Pergonal®, menotropins, USP (Serono) and Humegon™, menotropins, USP (Organon). ORG 32489 for Injection is indicated for the treatment of female infertility by inducing follicular growth and maturation and gonadal steroid production. ORG 32489 for Injection may also be used to stimulate the development of multiple follicles in women participating in an *in-vitro* fertilization program.

ii. Dosage Regimen

The dose of ORG 32489 for Injection must be individualized for each patient. On the basis of body weight in the treatment of female infertility, the most commonly used daily dose of 37.5 to 300 IU corresponds to approximately 0.625 to 5 IU/kg. The dosing period will be limited to 2 to 3 weeks for *in-vitro* fertilization cycles and 6 weeks for ovulation induction cycles. The maximum number of treatments is considered to be 20 to 30.

iii. Drug Absorption/Metabolism

The absorption of the active ingredient, recFSH, of ORG 32489 for Injection is slow and incomplete after administration. Absolute bioavailability values for single dose administration were between 42% and 58%. After intramuscular administration, an elimination half-life for recFSH of approximately 11 hours was obtained.

C. Site of Drug Substance Production and Environmental Settings

ORG 32489 will be manufactured by

a town of 50,000 inhabitants. The factory is located on a 160,000 square meter site together with other properties of the Organon group including research and development laboratories, technical services offices, control laboratories, etc. The site borders a meat canning company, a railway station, a housing development, and administrative offices.

D. Site of Drug Product Production and Environmental Settings

ORG 32489 for Injection will be manufactured by Organon Inc., 375 Mount Pleasant Avenue, West Orange, New Jersey 07052. The facility is situated on property bordering an electric utilities substation, a municipal golf course, an electric utilities switching station, an office building and condominiums. ORG 32489 for Injection will be packaged and distributed by Organon Inc., 6350 Hedgewood Drive, Allentown, Pennsylvania 18105. The facility borders several storage warehouses in an industrial park.

The following materials will be used in the packaging of ORG 32489 for Injection:

i. Container

Item:	Tubing vial, 2 mL (flint)
Material:	USP borosilicate glass
Neck Finish:	13 mm
Manufacturer:	

ii. Closure

Item:	13 mm stopper for lyophilization
Style:	West V-50
Compound:	4416/50 gray
Manufacturer:	

iii. Seal

Type:	Aluminum flip-off seal
Color:	To be determined
Manufacturer:	

E. Site of Drug Product Use and Disposal

ORG 32489 for Injection reconstituted with Sodium Chloride Injection 0.45% will be used by physicians in hospitals, clinics and medical offices. The product will be injected by medical personnel or may be dispensed to patients by prescription. Disposal of used syringes and vials by medical personnel or patient using the product, to the best of Organon Inc.'s knowledge, will be in compliance with federal, state and local statutes and regulations.

iii. Cardboard and paper are shredded by:

iv. The current waste disposal firms for the facility are:

5. Identification of Chemical Substances that are the Subject of the Proposed Action:

The nomenclature, chemical and physical properties of the drug substance in ORG 32489 for Injection is given below.

Laboratory Code Names:	
Active Ingredient:	recFSH
Lyophilzied Drug Substance:	ORG 32489
Chemical Name:	recombinant FSH
CAS Number:	9002-68-0
USAN Name for Active Ingredient:	Follitropin beta
INN Name for Active Ingredient:	Follitropin beta
Appearance:	White to off-white cake or powder free from visible impurities
Composition:	Each 50-mL vial of ORG 32489 drug substance contains approximately 100,000 IU recFSH and 200 mg of a mixture of sodium citrate:sucrose in a ratio of 0.46:1.54

Organon Inc. considers ORG 32489 for Injection to be non-hazardous. Material Safety Data Sheets for all inactive ingredients are provided in ATTACHMENT B. Since ORG 32489 for Injection is considered non-hazardous, permits are not required for disposal.

Expired and/or rejected drug product will be returned to Organon Inc., West Orange, New Jersey, where the materials are size reduced in a material shredder. Sawdust is added when necessary as an absorbent. The shredded materials are disposed of in an on-site dumpster which is collected by a contracted waste hauler. The waste is transported to the where it is destroyed or transferred to to be disposed in a landfill designated by the State. Unused packaging materials generated by the facility which do not identify the product or Organon Inc. are disposed of in the municipal trash except cardboard which is sent to a recycler. Packaging materials indicating the product or Organon Inc. are returned to the West Orange facility where they are destroyed as mentioned above.

Listed below are the firms proposed for disposal activities.

i. The current waste hauler for the West Orange, New Jersey facility is:

ii. The waste is destroyed by either:

This facility is operated by:

Or by:

6. Introduction of Substances into the Environment:

This section has been formatted according to the CFR format for an abbreviated Environmental Impact Assessment for a naturally occurring product.

As stated in Section 4.C, the manufacturer of the drug substance, ORG 32489, will be Therefore, no environmental release resultant of this operation is expected in the United States. The air emission from the production area to the surrounding environment is regulated by the National Nuisance Act in the Netherlands. The clean-up water, which may contain waste obtained from the cleaning process, is cooled and pretreated according to regional permissions, and in accordance with the Water Pollution Act in The Netherlands, and is discharged to the waste water treatment company. ATTACHMENT A contains letters certifying that is in compliance with applicable air and water emissions requirements and has been granted authority to produce and distribute ORG 32489 drug substance by the Dutch authorities.

During the production of ORG 32489 for Injection, the following chemical substances may be released into the occupational, atmospheric, and aquatic environments from the manufacturing and equipment cleaning processes. Material Safety Data Sheets (MSDS) for each of the chemical substances are provided in ATTACHMENT B.

Drug Substance

ORG 32489

Inactive Ingredients

- Sucrose, USP
- Polysorbate 20, USP
- Sodium Citrate, Dihydrate, USP
- Hydrochloric Acid, NF
- Sodium Hydroxide, NF

Process flow diagrams for ORG 32489 for Injection, presented in CONFIDENTIAL APPENDIX I, provide information for the processing of the chemical substances used to manufacture the drug product. In the manufacturing process, the weighing of dry chemicals and dispensing of liquid chemicals to prepare the batch, the processing of these chemicals into the bulk solution, and the equipment and room cleaning processes could allow for the release of wastes from the Sterile Production manufacturing area into the environment. A detailed description of the environmental controls employed during the manufacture of ORG 32489 for Injection is provided in CONFIDENTIAL APPENDIX II.

The wastes generated by filtering the process air and the filtering of the dust suction system used in the equipment and room cleaning processes are collected as residues on the air filters and are incinerated off-site at a regional incineration company. The air emission from the manufacturing area to the outside environment is regulated by the Department of Environmental Protection. The clean-up water, which may contain waste obtained from the cleaning process, is diluted, neutralized and discharged into the public sewer for transport to the waste water treatment company. The disposal of the wiping cloths used during clean-up is carried out by way of routine refuse removal.

A statement confirming Organon Inc.'s compliance with all federal, state and local environmental laws is provided in ATTACHMENT C. The approval of this application will have no effect upon Organon Inc.'s compliance with current emission requirements.

It is expected that sales of ORG 32489 for Injection will replace sales of the currently marketed drug products Metrodin®, urofollitropin (Serono), Pergonal®, menotropins, USP (Serono) and Humegon™, menotropins, USP (Organon). Therefore, the net increase of follicle stimulating hormone entering the environment should be negligible, if any.

7. **Fate of Emitted Substances in the Environment:**

This section has been formatted according to the CFR format for an abbreviated Environmental Impact Assessment for a naturally occurring product.

Through the clinical use of ORG 32489 for Injection, follicle stimulating hormone may enter the environment through the urine and bile (feces) of the user. The concentration of these components released into the environment through human excrement will displace already existing concentrations released from the currently marketed drug products. These concentrations are further diminished when combined with other water-carried wastes (i.e. storm water) which enter the public sewerage and/or waste water treatment systems. Disposal of unused ORG 32489 for Injection is accomplished by incineration through a contracted, EPA-regulated waste management company.

8. **Environmental Effects of Released Substances:**

This section has been formatted according to the CFR format for an abbreviated Environmental Impact Assessment for a naturally occurring product.

The follicle stimulating hormone used in ORG 32489 for Injection is produced by a Chinese hamster ovary (CHO) cell line and transfected with a plasmid containing the two subunit genes encoding human follicle stimulating hormone. It is purified from the CHO cell structure supernatant. The active substance is of high biochemical purity (≥ 99%) and a high specific biological activity. The starting materials are of non-human origin and well controlled. This precludes the presence of human derived contaminants. The follicle stimulating hormone of ORG 32489 for Injection will join naturally occurring follicle stimulating hormone which is normally released into the environment in low concentrations by pregnant and post-menopausal women. At present, no adverse environmental effects on animals, plants, humans, and other organisms have been recognized as a result of, or attributed to, the use of follicle stimulating hormone. It is anticipated that no adverse short or long-term side effects are predicted as a consequence of the release of ORG 32489 for Injection into the environment at levels associated with its production, use and/or disposal.

9. **Use of Resources and Energy:**

The impact of ORG 32489 for Injection including the packaging components on the use of resources and energy is nominal and is not excessive. The raw materials utilized to manufacture ORG 32489 for Injection are common compounds, all of which are in ample commercial supply. Only very small increases in the utilization of energy is anticipated since production occurs at an existing facility. The expected product volume will not significantly increase the consumption of those resources beyond present levels.

No effects upon endangered or threatened species and upon property listed in or eligible for listing in the National Register of Historic Places are anticipated.

10. **Mitigation Measures:**

No known potential adverse environmental impact exists for current follicle stimulating hormone products or for ORG 32489 for Injection.

The manufacture, distribution, use and disposal of ORG 32489 for Injection takes place under highly regulated and controlled conditions which further mitigate against negative environmental consequences.

11. **Alternatives to the Proposed Action:**

Not applicable since potential adverse environmental impacts brought on by the production, use, and/or disposal of ORG 32489 for Injection have not yet been identified.

12. **Preparers:**

Donald F. Bauch
Director, Manufacturing Technology
Technical Services Department
Organon Inc.
B.S., Mechanical Engineering Technology, 1995
N.J. Institute of Technology
Newark, New Jersey

Jenine S. Mason
Assistant Manager, Documentation
Pharmaceutical Development Department
Organon Inc.
B.A., Biochemistry, 1987
Rutgers University/Douglass College
New Brunswick, New Jersey

Edwina L. Muir
Manager, Regulatory Affairs
Organon Inc.
M.S., Biology, Pharmaceutical Marketing, 1993
Fairleigh Dickinson University
Rutherford, New Jersey

Jay L. Rheingold
Assistant Director, Pharmaceutical Development Department
Organon Inc.
Ph.D., Pharmaceutics, 1980
University of Connecticut
Storrs, Connecticut

Philip W. Stern
Director, Pharmaceutical Development Department
Organon Inc.
Ph.D., Pharmaceutical Chemistry, 1971
University of Michigan
Ann Arbor, Michigan

Ronald Zesch
Site Manager
Organon Inc., Allentown
MBA, Management, 1990
Fairleigh Dickinson University
Rutherford, New Jersey

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 preparation of the environmental assessment.

Patrick J. Osinski Nov. 19, 1995
Patrick J. Osinski Date
Vice President, Product Development and Government Affairs

14. **Reference:**

Environmental Impact Assessment Report, PDR-013, for Humegon™ Injection, NDA No. 20-328.

MATERIAL SAFETY DATA SHEET

no. 96.462

DIOSYNTH B.V. P.O. Box 20 5340 BH Oss The Netherlands, Emergency Tel. 31(0)412-661600 Tel. 31(0)412-661333
DIOSYNTH INC. 2745 Nth. Elston Avenue Chicago Illinois 60647-2020 USA, Tel. 312-235-7500 Telefax. 312-235-7504

SECTION I

CHEMICAL NAME AND SYNONYMS:	Recombinant FSH; Follitropin beta
CAS NO.:	169108-34-3 FORMULA: --
COMMON NAME:	ORG 32489

SECTION II - HAZARDOUS INGREDIENTS

MATERIAL/COMPOSITION:	Not applicable.	NATURE OF HAZARD:	

SECTION III - PHYSICAL DATA

MELTING POINT:	Not listed.	SPECIFIC GRAVITY:	Not applicable.
SOLUBILITY IN WATER:	Soluble.	BOILING POINT:	Not applicable.
VAPOUR PRESSURE (mm Hg):	Not applicable.	VOLATILE BY VOLUME %:	Not applicable.
VAPOUR DENSITY (AIR = 1):	Not applicable.	EVAPORATION RATE:	Not applicable.
APPEARANCE:	White to almost white amorphous powder, or cake.		

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

FLAMMABLE LIMITS:	LOWER: Not applicable. UPPER: Not applicable.
FLASH POINT (method used):	Not applicable.
FIRE EXTINGUISHING MEDIA:	Water, extinguishing powder, carbon dioxide or foam
SPECIAL FIRE FIGHTING PROCEDURES:	Evacuate personnel to safe area. Fire-fighters should use self-contained breathing equipment and protective clothing.
UNUSUAL FIRE AND EXPLOSION HAZARDS:	Ground mechanical equipment in contact with dry material to dissipate the potential build up of static electricity as prevention against dust explosion.

SECTION V - HEALTH HAZARD DATA

THERAPEUTICAL CATEGORY:	Pituitary hormone/ Gonadotrophic	THRESHOLD LIMIT VALUE:	None established

HAZARDS:	Routes of exposure: Inhalation, mucous membrane absorption and ingestion Effects of over-exposure: Effects on fertility; gynaecomastia. Acute effects: No acute toxicity data available; Symptoms of exposure may include: headache; tiredness. Chronic effects: May cause reproductive effects based on tests with laboratory animals; Scu-rat TDLo: 2 mg/kg (2D prior to copulation): REP. Addional: May cause sensitization by inhalation and skin contact; Allergic reactions to inhaled dust.
FIRST AID PROCEDURES:	Inhalation : Remove from exposure to fresh air. If breathing is difficult call a physician (show this Material Safety Data Sheet). Skin : Flush with copious amounts of water while removing contaminated clothing and shoes. Eyes : Flush with copious amounts of water for at least 15 minutes, separating eyelids with fingers. Transport to a physician (send this Material Safety Data Sheet with the patient). Ingestion : Wash out mouth with water provided person is conscious. Don't induce vomiting. Call a physician (show this Material Safety Data Sheet).

SECTION VI - REACTIVITY DATA			
STABILITY:	The product is stable.	CONDITIONS TO AVOID:	Not applicable.
INCOMPATIBILITY (Materials to avoid):		None.	
HAZARDOUS DECOMPOSITION PRODUCTS:		None.	
HAZARDOUS POLYMERIZATION:	Will not occur.	CONDITIONS TO AVOID:	Not applicable.

SECTION VII - SPILL OR LEAK PROCEDURES	
SPILLS:	Vacuum or sweep up spillage and transfer into an appropriate container for waste disposal and close effectively. Avoid dust. Ventilate area and wash spill site.
DISPOSAL:	Disposal on chemical waste dump site or by incineration according to Federal-, State- or local laws.

SECTION VIII - SPECIAL PROTECTION			
RESPIRATORY PROTECTION:	Dustmask (e.g. 3M no. 8710).		
VENTILATION:	LOCAL: Recommended. GENERAL: Recommended. (Mechanical)	SPECIAL: Not applicable. OTHER: Not applicable.	
PROTECTIVE GLOVES:	Chemically compatible.	EYE PROTECTION:	Goggles.
OTHER PROTECTIVE EQUIPMENT:	Wear a clean well fitted and closed overall. Change daily.		

SECTION IX - STORAGE CONDITIONS, HANDLING PRECAUTIONS	
HANDLING AND STORING:	Eating, drinking or smoking near material is forbidden. Store at - 20 °C in airtight containers to exclude micro-organisms and protected from light and moisture. Avoid breathing of dust. In case of skin contact showering is necessary with lots of water and soap. When grinding or micronising material a supplied air respirator (hood fit type) has to be used. Protect exposed skin. After finishing work showering is necessary.

SECTION X - ADDITIONAL INFORMATION
Toxicity Data: N.I. SAX et al. (7 Ed), 1989, p. 1763; RTECSno. (FSH): LP6330000

The information contained in this document is to our best knowledge true and accurate but all data, instructions, recommendations and/or suggestions are made without guarantee.

THIS SHEET SUPERSEDES MSDS NO. — DATED: —

DATE ISSUED 2/9/96

SIGNATURE

ATTACHMENT C

STATEMENT OF COMPLIANCE

Organon Inc. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of ORG 32489 for Injection at its facility in West Orange, New Jersey, as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the production of ORG 32489 for Injection at its facility in West Orange, New Jersey.