CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Chemistry Review(s)

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20825/000**
Priority: **1S**
Org Code: **120**
Stamp: **17-MAR-1997** Regulatory Due: **10-SEP-2000**
Action Goal:
District Goal: **15-NOV-1997**
Applicant: **PFIZER MEDICINAL**
EASTERN POINT RD
GROTON, CT 06340
Brand Name: **(ZIPRASIDONE HCL)20/40/60/80MG CA**
Established Name:
Generic Name: **ZIPRASIDONE HCL**
Dosage Form: **CAP (CAPSULE)**
Strength: **20, 40, 60, 80 MG**

FDA Contacts:
S. HARDEMAN (HFD-120) 301-594-2850 , Project Manager
R. SEEVERS (HFD-120) 301-594-2850 , Review Chemist
R. SEEVERS (HFD-120) 301-594-2850 , Team Leader

Overall Recommendation:

ACCEPTABLE on 24-JUL-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 26-MAY-1998 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 16-DEC-1997 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 19-NOV-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-APR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities:

Establishment:
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities:

Establishment: **1211022**
PFIZER INC
EASTERN POINT RD
GROTON, CT 06340
DMF No:
AADA No:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-JUL-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **2410924**
PFIZER INC
630 FLUSHING AVE
BROOKLYN, NY 11206
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-APR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9611016**
PFIZER PHARMACEUTICALS INC
RINGASKIDDY, COUNTY CORK, EI
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-APR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE** Responsibilities:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL

for May 19, 1998

Application: NDA 20825/000
Stamp: 17-MAR-1997 Regulatory Due: 17-JUN-1998
Applicant: PFIZER MEDICINAL
EASTERN POINT RD
GROTON, CT 06340

Priority: 1S Org Code: 120
Action Goal: District Goal: 15-NOV-1997
Brand Name: (ZIPRASIDONE HCL)20/40/60/80MG CA
Established Name:
Generic Name: ZIPRASIDONE HCL
Dosage Form: CAP (CAPSULE)
Strength: 20, 40, 60, 80 MG

FDA Contacts: S. HARDEMAN (HFD-120) 301-594-2850 , Project Manager
M. GUZEWSKA (HFD-120) 301-594-5571 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 16-DEC-1997 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 19-NOV-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: ,
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 16-DEC-1997
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW
Responsibilities:

Establishment:
DMF No:
AADA No:

Profile: CHG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 19-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities:

Establishment: 1211022
PFIZER INC
EASTERN POINT RD
GROTON, CT 06340
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 19-JUN-1997
Responsibilities: DRUG SUBSTANCE MANUFACTURER

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-825

CHEM. REVIEW # 3 **REVIEW DATE** 18-MAY-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	18-MAR-97	19-MAR-97	
AMENDMENT .N(BC)	02-MAY-97	05-MAY-97	
AMENDMENT .N(BC)	28-JUL-97	29-JUL-97	
AMENDMENT .N(BC)	23-OCT-97	24-OCT-97	
AMENDMENT .N(BZ)	24-OCT-97	27-OCT-97	
AMENDMENT .N(BC)	29-OCT-97	31-OCT-97	
AMENDMENT .N(BC)	31-OCT-97	13-NOV-97	
AMENDMENT .N(BL)	01-MAY-98	04-MAY-98	06-MAY-98

NAME AND ADDRESS OF APPLICANT PFIZER, Inc.
Eastern Point Road, Groton, CT 06340

DRUG PRODUCT NAME
Proprietary:
USAN [1994]: Ziprasidone Hydrochloride
Code Name/Number: CP-88,059-1
Chem. Type/Ther. Class:

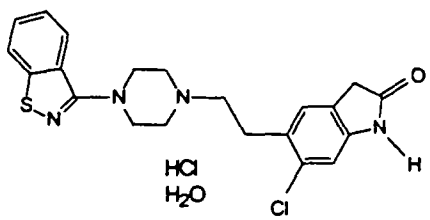
PHARMACOLOGICAL CATEGORY/INDICATION Psychosis
DOSAGE FORM Capsules
STRENGTHS 20, 40, 60 and 80 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone monohydrochloride, monohydrate

$C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$

Mol. Wt. 467.42 (412.94 + 36.46 + 18.02)

CAS Registry #: 138982-67-9



SUPPORTING DOCUMENTS: IND[ ]and 13 DMFs for container/closure systems
RELATED DOCUMENTS: Patent No. 4,831,031 (Expiration Date: March 2, 2007)
CONSULTS: The proposed trademark is acceptable by the CDER Labeling and Nomenclature Committee. The CGMP status of all manufacturing facilities is acceptable as of 16-DEC-97 ( ). The EA information is acceptable. The MV package is in preparation.
REMARKS/COMMENTS: This submission provides additional carton labeling for professional sample bottles of 14 capsules. The enclosed additional labels reflect revised NDC codes and identify Pfizer's U.S. Pharmaceuticals group as the responsible sales division rather than . These changes will also be applied to the professional sample labeling which was supplied with the original NDA. All other label text, color and layout remains unchanged. Also supplied are updated carton labels for hospital unit dose packaging which now reflect a unit of 80 capsules per carton rather than 100 capsules as was indicated in the original NDA. All other label text, color and layout remains unchanged. A detailed listing of the labels supplied with this submission is attached. The proposed expiration dating period of months is acceptable. The recommended storage conditions should read: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. The recommended by Biopharm dissolution methodology is as follows: a) Tier I Test: USP (paddle), 75 rpm, 900 mL (2% sodium dodecyl sulfate-SDS, 0.05 M NaH_2PO_4 buffer, pH 7.5), 37°C, Q = NLT % in 45 min; b) Tier II Test: USP (paddle), 75 rpm, 700 mL (1% pancreatin in 0.05 M NaH_2PO_4 buffer pH 7.5), 37°C. After 15 min incubation, 200 mL of phosphate buffer containing 9% of SDS is added to the medium, Q = NLT % in 45 min.
CONCLUSIONS & RECOMMENDATIONS: Recommend APPROVAL of NDA 20-825, as amended.

cc: Orig. NDA 20-825
HFD-120
HFD-120/MGuzewska 5.19.98
HFD-120/SHardeman

M. Guzewska, Ph.D., Chemist

Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: 2410924
PFIZER INC
630 FLUSHING AVE
BROOKLYN, NY 11206

DMF No:
AADA No:

Profile: CHG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 19-NOV-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: 9611016
PFIZER PHARMACEUTICALS INC
RINGASKIDDY
COUNTY CORK, , EI

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 19-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment:

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 19-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: CHG OAI Status: NONE

Responsibilities:

for May 19, 1998

Last Milestone:	**OC RECOMMENDATION**
Milestone Date	**23-JUN-1997**
Decision:	**ACCEPTABLE**
Reason:	**BASED ON PROFILE**

APPEARS THIS WAY
ON ORIGINAL

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commercial

information

for February 21, 1998

Application: NDA 20825/000
Stamp: 17-MAR-1997 Regulatory Due: 17-JUN-1998
Applicant: PFIZER MEDICINAL
EASTERN POINT RD
GROTON, CT 06340

Priority: 1S
Action Goal:
Brand Name:
Established Name:
Generic Name: ZIPRASIDONE HCL
Dosage Form: CAP (CAPSULE)
Strength: 20, 40, 60, 80 MG

Org Code: 120
District Goal: 15-NOV-1997
(ZIPRASIDONE HCL)20/40/60

FDA Contacts: S. HARDEMAN (HFD-121) 301-594-2850 , Project Manager
M. GUZEWSKA (HFD-120) 301-594-5571 , Review Chemist

Overall Recommendation:

WITHHOLD on 19-NOV-1997 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 16-DEC-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDAT 16-DEC-1997
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW
Responsibilities:

Establishment:
DMF No:
AADA No:

Profile: CHG OAI Status: NONE
Last Milestone: OC RECOMMENDAT 19-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities:

Establishment: 1211022
PFIZER INC
EASTERN POINT RD
GROTON, CT 06340
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDAT 19-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: 2410924
PFIZER INC
DMF No:

2410924
PFIZER INC
630 FLUSHING AVE
BROOKLYN, NY 11206

AADA No:

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Profile: CHG OAI Status: NONE
Last Milestone: OC RECOMMENDAT 19-NOV-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: 9611016
PFIZER PHARMACEUTICALS INC
RINGASKIDDY
COUNTY CORK, , EI

DMF No:

AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDAT 19-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Establishment:

DMF No:

AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDAT 19-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

Establishment:

DMF No:

AADA No:

Profile: CHG OAI Status: NONE
Last Milestone: OC RECOMMENDAT 23-JUN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120 JUL 18 1997
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-825

CHEM. REVIEW # 1 **REVIEW DATE** 03-JUL-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	18-MAR-97	19-MAR-97	28-MAR-97
AMENDMENT .N(BC)	02-MAY-97	05-MAY-97	08-MAY-97

NAME AND ADDRESS OF APPLICANT PFIZER, Inc.
Eastern Point Road, Groton, CT 06340

DRUG PRODUCT NAME
Proprietary: ™
Nonproprietary/USAN: Ziprasidone Hydrochloride
Code Name/Number: CP-88,059-1
Chem. Type/Ther. Class:

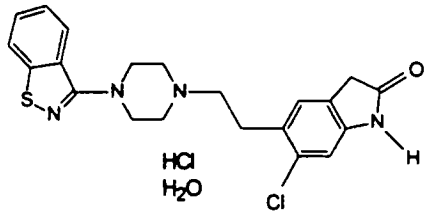
PHARMACOLOGICAL CATEGORY/INDICATION Psychosis
DOSAGE FORM Capsules
STRENGTHS 20, 40, 60 and 80 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, monohydrochloride, monohydrate

$C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$

Mol. Wt.– 467.42 (412.94 + 36.46 + 18.02)

CAS Registry #: 138982-67-9



SUPPORTING DOCUMENTS: IND [redacted] and 13 DMFs for container/closure systems
RELATED DOCUMENTS: Patent No. 4,831,031 (Expiration Date: March 2, 2007)
CONSULTS: The proposed trademark [redacted] is ACCEPTABLE by the CDER Labeling and Nomenclature Committee. The EER was sent out on 19-JUN-97 (copy attached). The EA review is pending (HFD-357). The MV package is in preparation.
REMARKS/COMMENTS: The CM&C information provided for ziprasidone HCl H_2O drug substance and ziprasidone capsules is adequate with the exception of stability data for the drug product. As agreed to in the pre-NDA meeting, an updated stability report and statistical analysis of stability data for ziprasidone capsules will be provided in Fall 1997. The 1X batch has been determined as [redacted] based on the sizes of stability and biobatches of the 20 mg capsules. The chemistry information on Amendment of 02-MAY-97 addresses the toxicity data for [redacted] a starting material carried forward as an impurity in the manufacturing of ziprasidone. Pfizer concludes that [redacted] at a specification level of [redacted]% does not represent a safety issue for patients receiving the maximum recommended daily dose of ziprasidone. The REVIEW NOTES are attached.
CONCLUSIONS & RECOMMENDATIONS: The CM&C information is not approvable at this time because stability data for ziprasidone capsules are incomplete. Pfizer made a commitment to amend the application in September 1997 to include the following: 1. Updated stability results for all strengths of capsules, 2. Assay results for the "crossover" point, and 3. Statistical analysis of stability data for ziprasidone capsules. Recommendation regarding the proposed expiration dating period will be made after the review of the amended stability data.

/S/
M. Guzewska, Ph.D., Chemist

cc: Orig. NDA 20-825
HFD-120
HFD-120/MGuzewska
HFD-120/SHardeman
HFD-120/SBlum
HFD-810/CHoiberg
HFD-810/JSimmons
R/D Init by: SWB

SWB 7/18/97

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JUL 25 1997

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

(ZIPRASIDONE HYDROCHLORIDE)
Capsule
NDA 20-825

Pfizer Inc

U. S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Neuropharmacological Drug Products
(HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-825

(Ziprasidone Hydrochloride)

Capsule

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 , Pfizer Inc has prepared an environmental assessment (attached) in accordance with *21 CFR 25.31a(a)*, which evaluates the potential environmental impact 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*.

Ziprasidone Hydrochloride is a chemically synthesized drug which is administered as a capsule in the treatment of schizophrenia. The drug substance will be manufactured by Pfizer Inc, Groton, Connecticut and Pfizer Pharmaceuticals Production Corporation, County Cork, Ireland. The finished drug product will be used as a prescription agent, primarily in home-use throughout this country.

Ziprasidone Hydrochloride drug substance may enter the environment from excretion by patients, from disposal of pharmaceutical waste or 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. Returned or out-of-specification drug substance and rejected 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. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

/s/

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

7/25/97
Date

/s/

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

7/25/97
Date

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

ENVIRONMENTAL ASSESSMENT

NON-CONFIDENTIAL [FREEDOM OF INFORMATION ACT (FOIA)] SUBMISSION

(Referenced Confidential Information Has Been Provided in a Separate Jacket)

Capsules
NOA 20-825
ziprasidone hydrochloride monohydrate

NDA # 20-825

March 15, 1997

Pfizer Inc
235 East 42nd Street
New York, NY 10017

3 0804

1. DATE
2. NAME OF APPLICANT/PETITIONER
3. ADDRESS
4. DESCRIPTION OF PROPOSED ACTION
   a. Requested Approval
   b. Need for the Action
   c. Production Locations
   d. Locations of Use
   e. Disposal Sites
5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION
      a. Nomenclature
      b. Chemical Abstracts Service (CAS) Registration Number
      c. Molecular Formula
      d. Molecular Weight
      e. Structural Formula
      f. Physical Description
      g. Additives
      h. Purity
   d. Discussion of the Effect of the Approval on Compliance With
6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT
   A. GROTON FACILITY (DRUG SUBSTANCES)
      a. Substances Expected to be Emitted
      b. Controls Exercised
      c. Citation of and Statement of Compliance with Applicable Emissions Requirements
      d. Discussion of the Effect of the Approval on Compliance With Current Emissions Requirements
   B. RINGASKIDDY FACILITY (DRUG SUBSTANCES)
      a. Substances Expected to be Emitted
      b. Controls Exercised
      c. Citation of and Statement of Compliance with Applicable Emissions Requirements
      d. Discussion of the Effect of the Approval on Compliance With Current Emissions Requirements
   C. BROOKLYN FACILITY (DRUG PRODUCTS)
      a. Substances Expected to be Emitted
      b. Controls Exercised
      c. Citation of and Statement of Compliance with Applicable Emissions Requirements
      d. Discussion of the Effect of the Approval on Compliance With Current Emissions Requirements
      e. Expected Introduction Concentrations
         i. Expected Introduction Concentration from Use
         ii. Expected Introduction Concentration from Disposal
7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT
   c. Tier 0
8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES
9. USE OF RESOURCES AND ENERGY
10. MITIGATION MEASURES
11. ALTERNATIVES TO THE PROPOSED ACTION
12. LIST OF PREPARERS
13. CERTIFICATION
14. REFERENCES
15. APPENDICES

15A. CONFIDENTIAL APPENDICES

ENVIRONMENTAL ASSESSMENT

Capsules

Ziprasidone Hydrochloride Monohydrate

Introduction- Pfizer Inc hereby submits an Environmental Assessment for Capsules (ziprasidone hydrochloride monohydrate) following the format prescribed in CDER's "Guidance for Industry for the Submission of an Environmental Assessment" dated November, 1995. This EA qualifies for the Tier 0 criterion, precluding the requirement for submission of format items 7, 8, 9, 10, 11 and 15, based on a production volume projection for a mature market.

In addition, the format and content and where appropriate, the exact wording of this EA follow precisely the format and content of the ARICEPT™ EA, Eisai America, Inc, NDA # 20-690, for which a Finding of No Significant Impact was issued for items 1; 2; 3; 4a; 4b; 4c[1]; 4d; 4e[1]; 5a-h; 6Aa,b,c,d; 6Ba,b,c,d; 6Ca,b,c,d; 6ei,ii; 7c[2]; 8; 9; 10; 11; 12[3]; 13[4]; 14; 15[5]; 15A,1,2,3,4,5,6,7[6].

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[1] with the exception that (i) only Pfizer facilities are relevant, and (ii) the Ringaskiddy facility had not been included in the ARICEPT™ EA, but the format and content for this facility specifically follow that for the Groton facility that had been included in the ARICEPT™ EA.

[2] with additional documentation that the projected introduction into the terrestrial environment through sludge-amendment to soil will also qualify for Tier 0.

[3] with the exception that only relevant Pfizer employees are listed

[4] with the exception that the certification statement also designates portions of the EA as non-confidential

[5] with the exception that only Pfizer-related regulations and permits are listed, with upgrading of permit expiry dates as appropriate

[6] with the exception that metabolism/excretion information is provided along with a corrected aquatic EIC and soil PEC based on sludge sorption data; see also footnote 1

1. **DATE:** March 15, 1997

2. **NAME OF APPLICANT/PETITIONER:** Pfizer Inc

3. **ADDRESS:** 235 East 42nd Street, New York, NY 10017

4. **DESCRIPTION OF PROPOSED ACTION:**

   a. Requested Approval. Pfizer Inc has filed NDA # 20-825 pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] Capsules (ziprasidone hydrochloride monohydrate), 20, 40, 60, 80, and 100 mg (as ziprasidone), packaged in suitable containers with appropriate seals: HDPE bottles containing desiccant with aluminum pulp vinyl liner/glassine seals; or unit dose aluminum foil blisters. The subject EA has been submitted pursuant to 21 CFR § 25.31a(a), following the Center for Drug Evaluation and Research "Guidance for Industry for the Submission of an Environmental Assessment" dated November, 1995.

   b. Need for the Action. [redacted]™ (ziprasidone hydrochloride monohydrate), the hydrochloride salt of a benzisothiazolyl-piperazine, is an antagonist to seratonin (5-HT_{2A}) and dopamine (D_2) receptors and has proved to be an effective antipsychotic agent for schizophrenia and other psychotic disorders. Ziprasidone hydrochloride will be used chronically. The total target population in the US is estimated to be at least 2.5 million patients.

   c. Production Locations. Manufacture of drug substance will be carried out at the Pfizer Inc, Groton, CT and Ringaskiddy, Ireland production facilities. Manufacture of drug product, including packaging, will be carried out at the Pfizer Inc, Brooklyn, NY facility. The intermediates listed in Confidential Appendix 4 are considered proprietary and are manufactured at the designated Pfizer Groton and Ringaskiddy facilities.

   The Groton facility [Pfizer Inc, Eastern Point Road, Groton, CT 06340] is located in an urban residential/industrial environment bounded on the north by the oil distribution facilities of Hess, Inc., on the east and south by single-family residences, and on the west by the Thames River. The topography is flat.

   The Ringaskiddy facility [Pfizer Pharmaceuticals Production Corporation, Ringaskiddy, Co. Cork, Ireland] is located in a semi-rural environment bounded on the north and east by Cork Harbor.

   The Brooklyn facility [Pfizer Inc, Brooklyn Plant, 630 Flushing Ave., Brooklyn, NY 11206-5092] is located in an urban environment in New York City in an area zoned for commercial use. South of the plant is a parking lot, to the east are multi-story tenements, to the west is a high-rise housing project, and to the north are vacant urban properties and industrial buildings. The topography is flat.

All locations are in temperate climates.

d. Locations of Use. ™ will be used as a prescription agent, primarily in home-use throughout the US.

e. Disposal Sites. Outdated or returned drug product (exclusive of returned samples) will be consolidated at the Pfizer Memphis Logistics Center, 1855 Shelby Oaks Drive North, Memphis, TN 38134 and shipped under manifest for disposal by high-temperature incineration to either of two disposal facilities which are licensed by an appropriate state authority to destroy hazardous and non-hazardous materials (Confidential Appendix 1).

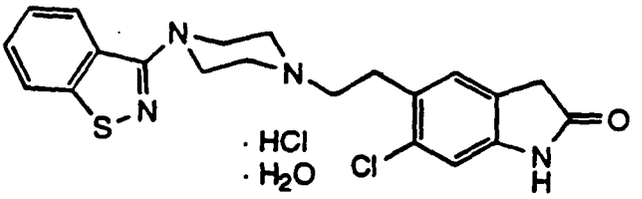
Returned samples of drug product will be consolidated at the Brooklyn facility [Pfizer Inc, 630 Flushing Ave., Brooklyn, NY 11206-5092] and shipped under manifest for disposal by high-temperature incineration at a facility licensed by an appropriate state authority to destroy hazardous and non-hazardous materials (Confidential Appendix 2).

Rejected/waste drug substance/drug product (and proprietary drug substance intermediates, where applicable) from the production facilities will be disposed-of by high-temperature incineration at facilities licensed by an appropriate state or national authority to destroy hazardous and non-hazardous materials (Confidential Appendix 3).

End-user disposal at US hospitals, pharmacies, or clinics of empty or partially-empty packages will follow hospital, pharmacy, or clinic procedures, and in the home empty or partially-empty containers will typically be disposed-of by a community's solid waste management system which may include landfills, incineration, and recycling, although minimal quantities of unused drug may be disposed-of in the sewer system.

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

a. Nomenclature:
   i. Established Name (U.S. Adopted Name - USAN): ziprasidone hydrochloride
   ii. Brand/Proprietary Name:
   iii. Chemical Name:
   Chemical Abstracts (CA) Index Name:
   5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate
b. Chemical Abstracts Service (CAS) Registration Number: [138982-67-9]
c. Molecular Formula: $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$
d. Molecular Weight: 467.42
e. Structural (graphic) Formula:



f. Physical Description: White/slightly pink powder, essentially free from visible foreign matter.

g. Additives (Drug Product): The drug product is a capsule comprised of drug substance formulated with pharmaceutically acceptable excipients (listed in EA format item 6.C.a., "Substances Expected to be Emitted"), available in 20, 40, 60, 80, and 100 mg strengths.

h. Purity: Pharmaceutical Grade, purity determined by assay (LC): 97.0% to 103.0% (anyhdrous, solvent free basis); total maximum level of impurities: 0.5%.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

Information on manufacture of ziprasidone hydrochloride monohydrate drug substance and drug product is delineated separately below for each facility, comprising a listing of controls exercised, citation of applicable site-related emissions regulations and requirements, statement of compliance with applicable emissions requirements, and discussion of the effect of approval on current applicable emissions requirements. Refer to item 4.e. (Disposal Sites) for an outline of disposal methods and sites for rejected, expired, returned or waste drug substance, proprietary drug substance intermediates, and drug product.

A. GROTON FACILITY (DRUG SUBSTANCE)

a. Substances Expected to be Emitted. An assessment of potential emissions from manufacture of ziprasidone hydrochloride monohydrate drug substance into the atmospheric, aquatic and terrestrial environments has been carried out. Environmentally-insignificant amounts of drug substance and manufacturing process components, including proprietary drug substance intermediates and by-products, will be emitted into the atmospheric, aquatic and terrestrial environments from manufacture of drug substance, based on the processes employed and the controls applied, as delineated in Confidential Appendix 4. Organic-solvent-containing and other hazardous wastes are disposed of via licensed contract incineration facilities (Confidential Appendix 5).

b. Controls Exercised. Emissions controls are used in the manufacturing process to ensure compliance with occupational exposure limits and with general emissions requirements, specific standards (including priority pollutants and ozone depleting chemicals), permit limits, and contract requirements for the atmospheric, aquatic and terrestrial release environments.

i. Atmospheric. Air emissions from the manufacturing process comprising particulates, gases, and solvents will be controlled through the use of assorted filters and scrubbers. Emissions from liquid and gaseous handling systems also will be controlled via use of proper operational procedures (e.g., back-venting during solvent transfer) and properly designed condensing and scrubbing systems (e.g., vent condensers and substance-specific scrubbers). An end-of-line VOC emissions control device operates at greater than the permitted efficiency of 93%.

ii. Aqueous. Aqueous discharges from the manufacturing facility, comprising aqueous waste streams and equipment washings, will be pre-treated and disposed of using an on-site WWTF, which operates under an NPDES permit and achieves >95% reduction of influent process BOD, to ensure control of emissions to the aqueous release environment.

iii. Terrestrial. Hazardous wastes are disposed of via licensed contract facilities (Confidential Appendix 5). Non-hazardous solid wastes (other than those containing drug product and drug product intermediates which are disposed of as per Confidential Appendix 3), comprising filters and filter aids, disposable garments, etc., will be managed at licensed contract disposal facilities.

c. Citation of and Statement of Compliance with Applicable Emissions Requirements.

i. Compliance. The applicant certifies that emissions, discharges, and wastes from production ziprasidone hydrochloride monohydrate drug substance will be in compliance with applicable occupational health and safety standards and federal, state and local emissions regulations and permits, or with applicable consent orders and administrative orders and directives for the Pfizer Groton facility.

The MSDS for ziprasidone hydrochloride monohydrate drug substance is provided in Appendix 1.

ii. Permits. A citation (i.e., list of regulations/laws) of all applicable Federal, State, and local emissions requirements, including occupational, is provided in Appendix 2. A listing of permits, including the numbers, authorizing authorities, and expiration dates are provided in Appendix 3.

d. Discussion of the Effect of the Approval on Compliance With Current Emission Requirements. Approval of the proposed action will have a minimal effect upon compliance with existing emissions requirements at the Groton manufacturing site. For example, the Pfizer Groton

WWTF permit parameters are projected to be impacted by less than 1% of overall capacity; similarly for the facility's VOC air permit limits.

B. RINGASKIDDY FACILITY (DRUG SUBSTANCE)

a. Substances Expected to be Emitted. An assessment of potential emissions from manufacture of ziprasidone hydrochloride monohydrate drug substance into the atmospheric, aquatic, and terrestrial environments has been carried out. Environmentally-insignificant amounts of drug substance and manufacturing process components, including proprietary drug substance intermediates and by-products, will be emitted into the atmospheric, aquatic, and terrestrial environments from manufacture of drug substance, based on the processes employed and the controls applied, as delineated in Confidential Appendix 4. Organic-solvent-containing and other hazardous wastes are disposed-of via licenced contract incineration facilities (Confidential Appendix 5).

b. Controls Exercised. Emissions controls are used in the manufacturing process to ensure compliance with occupational exposure limits and with general emissions requirements, specific standards (including priority pollutants and ozone depleting chemicals), permit limits, and contract requirements for the atmospheric, aquatic, and terrestrial release environments.

i. Atmospheric. Air emissions from the manufacturing process comprising particulates, gases, and solvents will be controlled through the use of assorted filters and scrubbers. Emissions from liquid and gaseous handling systems also will be controlled via use of proper operational procedures (e.g., back-venting during solvent transfer) and properly designed condensing and scrubbing systems (e.g., vent condensers and substance-specific scrubbers). An end-of-line VOC emissions control device operates at greater than the permitted efficiency of 93%.

ii. Aqueous. Aqueous discharges from the manufacturing facility, comprising aqueous waste streams and equipment washings will be pre-treated and disposed-of using an on-site WWTF which operates under an Integrated Pollution Control License and achieves >95% reduction of influent process BOD to ensure control of emissions to the aqueous release environment.

iii. Terrestrial. Hazardous wastes are disposed of via licensed contract facilities (Confidential Appendix 5). Non-hazardous solid wastes (other than those containing drug product and drug product intermediates which are disposed-of as per Confidential Appendix 3), comprising filters and filter aids, disposable garments, etc., will be managed at licensed contract disposal facilities.

c. Citation of and Statement of Compliance with Applicable Emissions Requirements.

i. Compliance. The applicant certifies that emissions, discharges, and wastes from production of ziprasidone hydrochloride monohydrate drug substance will be in compliance with applicable occupational health and safety standards and federal, state, and local emissions regulations and permits, or with applicable consent orders and administrative orders and directives for the Pfizer Ringaskiddy facility.

The MSDS for ziprasidone hydrochloride monohydrate drug substance is provided in Appendix 1.

ii. Permits. A citation (i.e., list of regulations/laws) of all applicable Irish and Cork County emissions requirements, including occupational, is provided in Appendix 2. A listing of permits, including the numbers, authorizing authorities, and expiration dates are provided in Appendix 3.

d. Discussion of the Effect of the Approval on Compliance With Current Emission Requirements. Approval of the proposed action will have a minimal effect upon compliance with existing emissions requirements at the Ringaskiddy manufacturing site. For example, the Pfizer Ringaskiddy WWTF permit parameters are projected to be impacted by less than about 7% of overall capacity; similarly for the facility's VOC air permit limits.

C. BROOKLYN FACILITY (DRUG PRODUCT)

a. Substances Expected to be Emitted. An assessment of potential emissions from manufacture of [redacted]™ Capsules drug product into the atmospheric, aquatic, and terrestrial environments has been carried out. No significant emissions to the atmospheric, aquatic, and terrestrial environments associated with drug product manufacture - i.e., the milling, compacting, granulating, and blending of drug bulk and excipients; capsule-filling and packaging operations; and equipment clean-outs associated with [redacted]™ Capsules manufacture – are expected, based on (a) the efficiency of the operations in which virtually all usable product is consumed and (b) the controls applied, as outlined in Confidential Appendix 6. Moreover, there is no usage of organic solvents in manufacture of drug product.

b. Controls Exercised. Emissions controls are used in the manufacturing process to ensure compliance with occupational exposure limits and with general emissions requirements, specific standards (including priority pollutants and ozone depleting chemicals), permit limits, and

contract requirements for the atmospheric, aquatic, and terrestrial release environments.

i. Atmospheric. Air emissions from the manufacturing process are minimal and are restricted to specific processing areas. Particulate emissions will be controlled through the use of filters (HEPA and the like, with efficiencies of 99.9%) and scrubbers on powder systems. Filters are checked routinely, cleaned, and replaced as needed.

ii. Aqueous. Liquid discharges from the manufacturing process, comprising primarily equipment/facilities washings, will be pre-treated and disposed-of into a regional POTW (Newtown Creek) operating under NPDES permit to ensure control of emissions to the aqueous release environment.

iii. Terrestrial. Pharmaceuticals containing solid wastes are disposed-of via licensed contract facilities (Confidential Appendix 2). Non-hazardous wastes, comprising filters, disposable garments, packaging materials, etc., will be managed using off-site incineration at fully licensed contract facilities.

c. Citation of and Statement of Compliance with Applicable Emissions Requirements.

i. Compliance. The applicant certifies that emissions, discharges, and wastes from production of . ™ Capsule drug product will be in compliance with applicable occupational health and safety standards and federal, state, and local emissions regulations and permits, or with applicable consent orders and administrative orders and directives for the Pfizer Brooklyn facility.

The MSDS for ziprasidone hydrochloride monohydrate is provided in Appendix 1.

ii. Permits. A citation (i.e., list of regulations/laws) of all applicable Federal, State, and local emissions requirements, including occupational, is provided in Appendix 2. A listing of permits, including the numbers, authorizing authorities, and expiration dates are provided in Appendix 3.

d. Discussion of the Effect of the Approval on Compliance With Current Emission Requirements. Approval of the proposed action will have a minimal effect upon compliance with existing emissions requirements at the Brooklyn manufacturing site. For example, aqueous releases to the Newtown Creek POTW will be impacted by less than 1% of the Pfizer facility's liquid effluent permit parameters.

e. EXPECTED INTRODUCTION CONCENTRATIONS

i. Expected Introduction Concentration from Use. The expected introduction concentrations entering into the external aquatic ($EIC_{aquatic}$) and terrestrial (via sludge amendment to soil, $EIC_{terrestrial}$) environments have been calculated (Confidential Appendix 7) based on results of WWTF sludge sorption studies.

ii. Expected Introduction Concentration from Disposal. Not applicable (Reference 1, p. 15).

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT:

c. Tier 0. The Tier 0 criterion has been met (see Item 6.e.1), indicating that EA items 7, 8, 9, 10, 11, and 15 will not normally be needed (Reference 1, p. 18). In addition, the projected introduction concentration in the terrestrial environment is judged environmentally insignificant, not warranting documentation of fate and effects for the terrestrial environment (items 8 and 9).

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES: Not applicable. See Item 7 above.

9. USE OF RESOURCES AND ENERGY: Not applicable. See Item 7 above.

10. MITIGATION MEASURES: Not applicable. See Item 7 above.

11. ALTERNATIVES TO THE PROPOSED ACTION: Not applicable. See Item 7 above.

12. LIST OF PREPARERS:

Jon F. Ericson, Senior Research Scientist, Environmental Sciences Department, Pfizer Central Research Process Research and Development Department. Analytical Chemist with M.S. and 10 years experience in drug metabolism and environmental science.

Irving M. Goldman, Director, Environmental Sciences, Pfizer Central Research, Process Research and Development Department. Organic chemist with Ph.D. and 36 years experience in R&D on human drugs, process research, specialty chemicals, pharmaceutical research and regulatory affairs.

William D. Huhn, Senior Corporate Counsel, Pfizer Legal Division. Attorney with LLB and 19 years experience with Pfizer environmental legal compliance.

Charles M. Shafran, Director of Engineering, Pfizer Pharmaceuticals. Chemical engineer with M.Eng. (Chem.) and 25 years of experience in organic chemical production, engineering and environmental administration.

13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of Pfizer Inc's knowledge.

The undersigned official certifies that the subject EA summary document, Non-Confidential [Freedom of Information Act (FOIA)] Submission, contains non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Name: Irving M. Goldman, Ph.D.

Title:
Director, Environmental Sciences

Department:
Process Research and Development

Pfizer Central Research Groton, CT
06340

Irving M. Goldman
Signature

March 15, 1997
Date

14. REFERENCE:

1. "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements", Center for Drug Evaluation and Research (CDER), November 1995

15. APPENDICES:

1. MSDS for Ziprasidone Hydrochloride Monohydrate.
2. Applicable Exposure and Emissions Requirements for the Occupational, Atmospheric, Aquatic and Terrestrial Environments.
3. Applicable Permit Numbers, Issuing Authorities and Expiration Dates for U.S. Manufacturing Facilities

15A. CONFIDENTIAL APPENDICES:

1. Disposal Sites for Outdated or Returned Drug Product
2. Disposal Site for Returned Samples of Drug Product and Pharmaceuticals-Containing Solid Wastes from the Brooklyn Facility
3. Disposal Sites for Rejected/Waste Drug Substance/Drug Product and Proprietary Drug Substance Intermediates, Where Applicable
4. Potential Manufacturing Emissions into the Atmospheric (AT), Aquatic (AQ) and Terrestrial (TE) Environments -- Drug Substance
5. Disposal Sites for Organic-Solvent-Containing and Other Hazardous Wastes from the Groton and Ringaskiddy Facilities
6. Potential Manufacturing Emissions into the Atmospheric (AT), Aquatic (AQ) and Terrestrial (TE) Environments -- Drug Product
7. Basis for Expected Introduction Concentration from Use Into the External Aquatic and Terrestrial Environments

Appendix 1

MSDS Ziprasidone Hydrochloride Monohydrate

Central Research
Eastern Point Road
Groton, Connecticut 06340
Emergency Telephone: 860 441-4100

Experimental Substance Material Safety Data Sheet

October, 1996
[supercedes February, 1993]

MSDS #0184

[Ziprasidone Hydrochloride Monohydrate]
CP-88,059-01

[5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, monohydrochloride, monohydrate]

SECTION I: *PHYSICAL DATA*

Appearance:	Off white to tan or pink solid
Melting Point:	308 to 311°C
Molecular Weight:	467.4
Molecular Formula:	$C_{21}H_{21}ON_4ClS.HCl.H_2O$
Description:	Anti-psychotic candidate
Solubility:	Insoluble in water, slightly soluble in hot tetrahydrofuran
Storage Conditions:	CP-88,059-01 should be stored at ambient conditions protected from direct sunlight in tightly sealed containers.

SECTION II: *FIRE AND EXPLOSION HAZARD*

CP-88,059-01 does not present any unusual or significant fire hazards. If material becomes involved in a fire, it may be extinguished with appropriate extinguishing media, including water.

CP-88,059-01 has weak to moderate dust explosion characteristics based on the K_{st} value of 151 bar-m/sec determined from 20L sphere tests. The minimum ignition energy was 100-300 mJ for the sample indicating a relatively low sensitivity to ignition. The minimum ignition temperature was 640-660°C. The powder exhibits high chargeability and resistivity ($>1 \times 10^{14}$ ohm-m) with significant charge decay time (5.3 hours) making it a potential electrostatic hazard.

SECTION III: *HEALTH HAZARD DATA*

The approximate oral LD_{50} of CP-88,059-01 in rats and mice (both sexes) was greater than 2000 mg/kg. In addition, the rabbit dermal LD_{50} was determined to be greater than 2000 mg/kg. The potential for ocular irritation was also evaluated according to Federal Hazardous Substances Act (FHSA) guidelines; CP-88,059-01 is not an ocular irritant because a positive irritating reaction was not produced in any of the treated eyes at up to 72 hours post instillation of 44.9 mg. Based on the oral and dermal results, CP-88,059-01 would not be considered a Class B Poison or a poisonous material according to DOT guidelines or a harmful substance according to European guidelines when orally administered to rats, or applied to the skin of rabbits.

In a variety of *in vivo* and *in vitro* genetic toxicology assays, CP-88,059-01 was shown not to be mutagenic.

The toxicity profile of CP-88,059-01 has not been fully evaluated. It is imperative that all precautions to minimize exposure to CP-88,059-01 be employed. In 6 month studies, 10 mg/kg/day was considered to be the No Observed Adverse Effect Level (NOAEL) in rats, and 5 mg/kg/day was considered to be the NOAEL in dogs.

CP-88,059-01 did not produce any teratogenic effects in either the rabbit or the rat at doses up to 60 or 160 mg/kg, respectively.

SECTION IV: *FIRST AID INFORMATION*

Ingestion:	In the event of accidental ingestion of CP-88,059-01 (solid), medical attention should be summoned.
Inhalation:	Personnel who have accidentally inhaled CP-88,059-01 should be removed to fresh air and observed by medical personnel.
Skin/Eye Contact:	Flush copiously with water, summon medical attention.

SECTION V: *SPILL OR LEAK PRECAUTION*

Spills of CP-88,059-01 should be collected (scooped or swept) into appropriate recovery containers. Personnel involved in clean-up of spills, particularly solids, must wear respiratory protection, gloves and eye protection.

The area may be washed with water.

issued by: D. P. Brannegan

Appendix 2

Applicable Exposure and Emissions Requirements for the Occupational, Atmospheric, Aquatic and Terrestrial Environments

1. Occupational.- Workplace exposure will be in compliance with the following requirements:

    i. Groton and Brooklyn facilities:
    - Permissible Exposure Limits according to 29 CFR 1910.100

    ii. Ringaskiddy facility:
    - Permissible Exposure Limits as defined by the Republic of Ireland National Health and Safety Authority

2. Atmospheric.- Emissions will be in compliance with the following requirements:

    i. Groton facility:
    - Federal Clean Air Act and Regulations
    - Connecticut General Statutes Title 22a, Chapter 446c, Air Pollution Control Laws
    - CT DEP Air Pollution Control Regulations, Title 22a, Chapter 174
    - Connecticut State Implementation Plan
    - Resource Conservation and Recovery Act
    - RCRA Regulations 40 CFR Parts 260-268
    - Connecticut General Statutes Title 22a, Chapter 446d (Connecticut Solid Waste Management Acts), and Title 22a, Chapter 445 (Connecticut Hazardous Waste Law)
    - Connecticut Hazardous Waste Management Regulations, Title 22a, Chapter 449

    ii. Brooklyn facility:
    - Federal Clean Air Act and Regulations
    - New York State Air Pollution Regulations, Title 6, Chapter III, Subchapter A, Parts 201 through 212 and Part 233

    iii. Ringaskiddy facility:
    - Requirements for Integrated Pollution Control License, EPA

3. Aqueous.- Emissions will be in compliance with the following requirements:

    i. Groton facility:
    - Federal Clean Water Act
    - 40 CFR Parts 124 and 125 (Federal Clean Water Regulations)

- Connecticut General Statutes Title 22a, Chapter 446k, Water Pollution Control
- Connecticut DEP Discharge Permit Regulations, Title 22a, Chapter 430

ii. Brooklyn facility:
- Federal Clean Water Act
- Federal Clean Water Regulations, 40 CFR Parts 124 and 125
- New York City Charter, Section 1105, Administrative Code of New York City, Section 1403, Section 683e, Sections 687 and 689, New York City Bureau of Water Pollution Control
- New York City DEP Commissioner's Order and Directive for Effluent Pre-treatment, dated September 12, 1990

iii. Ringaskiddy facility:
- Requirements for Integrated Pollution Control License, EPA

4. Terrestrial.- Non-hazardous and hazardous waste emissions will be in compliance with the following requirements:

I. Groton facility:
- Resource Conservation and Recovery Act
- RCRA Regulations 40 CFR Parts 260-268
- Connecticut General Statutes Title 22a, Chapter 446d (Connecticut Solid Waste Management Acts), and Title 22a, Chapter 445 (Connecticut Hazardous Waste Law)
- Connecticut Solid Waste Management Regulations, Title 22a, Chapter 209
- Connecticut Hazardous Waste Management Regulations, Title 22a, Chapter 449

ii. Brooklyn facility:
- Resource Conservation and Recovery Act
- RCRA Regulations 40 CFR Parts 260-268
- New York Solid and Hazardous Waste Management Laws, New York Consolidated Laws Service; Environmental Conservation Law, Article 27
- New York Hazardous Waste Regulations, New York Compilation of Rules and Regulations, Title 6, Chapter 370, 371 and 372

iii. Ringaskiddy facility:
- Requirements for Integrated Pollution Control License, EPA

Appendix 3

Applicable Permit/License Numbers, Issuing Authorities and Expiration Dates

Permits for Brooklyn Facility:

Emission	Authorizing Agency	Permit Designation (Number)	Expiration Date
Water	NYC DEP	Industrial User Permit No. 95-P628-1	May 4, 2000
Air	NYC DEP	PA535/73Z	May 11, 1997
	NYC DEP	PA533/73Y	May 11, 1997
	NYC DEP	PA536/73X	May 11, 1997

Permits for Groton Facility:

Emission	Authorizing Agency	Permit Designation (Number)	Expiration Date
Water	CT DEP	NPDES Permit # CT0000957	July 30, 1996[1]
Air	CT DEP	Permit to Operate #0081	Issued December 14, 1995[2]
	CT DEP	RACT Order 8021	Issued August 15, 1995[3]
	CT DEP		

Permits for Ringaskiddy Facility:

Emission	Authorizing Agency	Permit Designation (Number)	Expiration Date
Air, Water, Waste	EPA	Integrated Pollution Control License #13	Issued May 18, 1995[4]

[1] Continues in effect until new permit issues
[2] No designated expiration date.
[3] Same as footnote 2
[4] Same as footnote 2

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

DIVISION OF YOURDIVISIONNAMEHERE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-825 **DATE REVIEWED:** 20-DEC-2000 **REVIEW #:** 4 **REVIEWER:**Seevers

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	18-MAR-1997	19-MAR-1997	
AMENDMENT	24-OCT-2000	25-OCT-2000	26-OCT-2000

NAME & ADDRESS OF APPLICANT: Pfizer, Inc.
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME

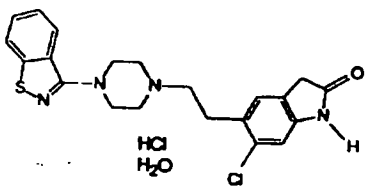
Proprietary:	™
Established:	ziprasidone HCl
Code Name/#:	MP-123456B
Chem.Type/Ther.Class:	1 Z

PHARMACOL. CATEGORY/INDICATION: Psychosis

DOSAGE FORM:	Capsules
STRENGTHS:	20, 40, 60, and 80 mg
ROUTE OF ADMINISTRATION:	WAYTOGIVEIT
Rx/OTC	x Rx ___ OTC
SPECIAL PRODUCTS:	___ Yes x N

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-[2-[4-(1,2-benzisothiazol-3yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone monohydrochloride, monohydrate



Mol. Wt. 467.42 (412.94 + 36.46 +18.02)

CAS Registry # 138982-67-9

SUPPORTING DOCUMENTS: see Review # 3

RELATED DOCUMENTS (if applicable): Patent # 4,831,031 (Expiration Date: March 2, 2007)

CONSULTS: Inspections were resubmitted March 29, 2000 and an overall recommendation of Acceptable was made on July 24, 2000

REMARKS: The October 24, submission consists of revised stability data tables for the drug substance and drug product. Specifically, during the pre-approval inspection .

were found in the NDA stability data tables. These errors have been corrected in the present submission and result in no change in the stability conclusions.

CONCLUSIONS & RECOMMENDATIONS: Recommend APPROVAL of NDA 20-825 from a CMC standpoint.

/S/ 12/20/00

Robert H. Seevers, Ph.D. Chemistry Team Leader