CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-744

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

CUROSURF®
(PORACTANT) pending
sterile solution for intratracheal administration

NDA 20-744

Dey Laboratories

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF PULMONARY DRUG PRODUCTS
(HFD-570)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-744

CUROSURF®

(Poractant) pending

sterile suspension for intratracheal administration

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 Curosurf®, Dey Laboratories 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*.

Poractant 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) . The drug substance will be manufactured by and the sterile drug product will be manufactured by Chiese Farmaceutici, S.p.A., Parma, Italy. The finished drug product will be used primarily in hospitals and clinics where premature infants are treated.

Poractant 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/

2/4/97
Date

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

/S/

2/4/97
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)

CONFIDENTIAL

SECOND REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-744
Curosurf®
(Poractant)
sterile suspension for intratracheal administration

Dey Laboratories

Division of Pulmonary Drug Products
(HFD-570)

CENTER FOR DRUG EVALUATION AND RESEARCH

SUMMARY OF ENVIRONMENTAL ASSESSMENT

The current review is of the amendment dated 1/16/97.

This drug complies with Infrequent Use, Orphan Drug, and Tier 0 criteria and was submitted in the Tier 0 format described in our recent Guidance to Industry. The firm states that the format conforms also to 21 CFR 25.31a(b)(3). The Chemical Type and Medical Potential are 1S. The drug product is derived from natural sources, porcine lungs, which makes it a naturally occurring pulmonary substance.

Administrative History

Original EA Date: June 1996
CDER Clock Date: 7/3/96
Filability accepted: 8/28/96
Logged into HFD-357: 9/5/96
Reviewer received: 9/13/96
Review dated: 9/24/96
Deficiency letter dated: 11/19/97
Amendment date: 1/16/97

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS

The only deficiency in the EA dated June 1996 was that Dey Laboratories did not sign off. With this amendment, that has been corrected.

We do not expect environmental damage from the production and use of this drug for the following reasons:

1. Poractant is a natural substance derived from extraction of porcine lungs. As such it is particularly non-corrosive and non-life threatening.

2. The amount used in this country is only about 6 kilos per year and any waste treatment plant can easily handle the substance.

3. Poractant qualifies for infrequent use, Orphan Drug, natural product, and Tier 0 status. The submitted EA is almost adequate for the Orphan Drug format.

RECOMMENDATIONS

Recommend that we write the FONSI for this NDA

ENVIRONMENTAL ASSESSMENT REVIEW
(Orphan, Infrequent Use, Tier 0)

1. **Date of EA Submission:**

   June 1996

   Betty Kuzmik, CSO/PM

   Adequate

2. **Name of applicant/petitioner:**

   APPEARS THIS WAY
   ON ORIGINAL

   Dey Laboratories

   Adequate

3. **Address:**

   2751 Napa Valley Corporate Drive
   Napa Valley, California 94558

   Adequate

REVIEW OF DEFICIENCY UNCOVERED IN FIRST REVIEW.

The only deficiency was that a Dey Laboratory representative did not sign off the EA. An adequate replacement page was submitted.

Adequate

APPEARS THIS WAY
ON ORIGINAL

/S/

2/4/97
Date

Prepared by
Carl J. Berninger, Ph.D.
Environmental Scientist
Center for Drug Evaluation and Research

/S/

2/4/97
Date

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

APPEARS THIS WAY
ON ORIGINAL

CONFIDENTIAL

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-744
Curosurf®
(Poractant)
sterile suspension for intratracheal administration

Dey Laboratories

Division of Pulmonary Drug Products
(HFD-570)

CENTER FOR DRUG EVALUATION AND RESEARCH

SUMMARY OF ENVIRONMENTAL ASSESSMENT

This drug complies with Infrequent Use, Orphan Drug, and Tier 0 criteria and was submitted in the Tier 0 format described in our recent Guidance to Industry. The firm states that the format conforms also to 21 CFR 25.31a(b)(3).

The Chemical Type and Medical Potential are 1S.

The drug product is derived from natural sources, porcine lungs, which makes it a naturally occurring pulmonary substance.

Administrative History

CDER Clock Date: 7/3/96
Filability accepted: 8/28/96
Logged into HFD-357: 9/5/96
Reviewer received: 9/13/96
Review Due Date: 12/02/96

CONCLUSIONS

We do not expect environmental damage from the production and use of this drug for the following reasons:

1. Poractant is a natural substance derived from extraction of porcine lungs. As such it is particularly none corrosive and none life threatening.

2. The amount used in this country is only about 6 kilos per year and any waste treatment plant can easily handle the substance.

3. Poractant qualifies for infrequent use, Orphan Drug, natural product, and Tier 0 status. The submitted EA is almost adequate for the Orphan Drug format.

However, Dey Laboratories does not certify the EA, and that needs correction.

RECOMMENDATIONS

Recommend that the Division notify Dey Laboratories of the need for an amended EA. See Deficiency Letter.

ENVIRONMENTAL ASSESSMENT REVIEW
(Orphan, Infrequent Use, Tier 0)

1. **Date of EA Submission:**

   June 1996

   Betty Kuzmik, CSO/PM

   Adequate

2. **Name of applicant/petitioner:**

   Dey Laboratories

   APPEARS THIS WAY
   ON ORIGINAL

   Adequate

3. **Address:**

   2751 Napa Valley Corporate Drive
   Napa Valley, California 94558

   Adequate

4. **Description of the proposed action:**

   a. **Requested Approval:**

   This first section explains the genesis of neonatal respiratory distress syndrome (RDS).

   Dey Laboratories is requesting the approval for Poractant, in vials of 1.5 and 3.0 mL fill volumes for distribution throughout the United States. Poractant is intended for the treatment and prophylaxis of neonatal respiratory distress syndrome (RDS).

   The draft labeling (package insert) gives complete information on how the drug is supplied and other information. The draft package insert is included in the non-confidential EA, but since it may be changed, it should not be included in the public EA.

This drug substance was first submitted to CDER under IND number

Adequate

b. **Need for Action:**

Information is given as to the use of this drug product. The estimated number of pediatric cases is 50,000 per year for this country. Curosurf® has been designated as an Orphan Drug by the FDA on August 2, 1993, application number

Adequate

c. **Production Locations:**

i. **Proprietary Intermediate(s):**

The firm's statement that "No intermediates are considered proprietary" is adequate. See page 3 (8).

ii. **Drug Substance:**

Non-confidential Appendix C provides signed certification that the is in compliance with all regulations and laws of
See page 37.

iii. **Finished Dosage Form:**

Manufactured and Packaged by:

Chiese Farmaceutici, S.p.A
Via Palermo 26/A
43100 Parma, Italy

Non-confidential Appendix C provides signed certification that the Chiese site is in compliance with all regulations and laws of Italy. See page 36.

Environmental site information is given for the above facilities.

Adequate

d. Expected Locations of Use (Drug Product):

Drug use will primarily be in hospitals throughout this country.

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e. Disposal Locations (Drug Product):

Disposal location information in Italy is not necessary because of the adequate compliance statement in appendix C.

"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 Curosurf® 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." See page 4 (9).

Disposition of returned or expired goods by the U.S. applicant is not specified, however any type of disposal system would be appropriate for this product.

The lipids extracted from porcine lungs are harmless to the environment.

Adequate

5. Identification of chemical substances that are the subject of the proposed action:

The MSDS is provided in the non-confidential portion of this EA.

Curosurf® is a natural pulmonary surfactant which has been extracted from porcine lungs by a combination of . It consists of approximately 99% polar liquids (mainly phospholipids) and 1 % hydrophobic, low molecular weight proteins (SP-B & SP-C).

The phospholipid fraction is made up of the following constituents: Phosphatidylcholine (primarily dipalmitoylphosphatidylcholine).

Drug Substance:

Chemical Name: 1, 2-Diacyl-SN-Glycero-3-Phosphoryl derivatives
Brand Name: Curosurf®
USAN Name: Poractant (submitted)
BAN: Poractant Alfa
CAS #: 96684-40-1
Laboratory Code Number: none given
Molecular Weight: NA
Molecular Formula: NA

Structural Formula: NA

Physical Description: white to off white suspension
Additives: none
Impurities: ppm levels of

Drug Product:

Composition: Given on page A-4 of the confidential EA section

Adequate

6. **Introduction of substances into the environment: For the site(s) of production:**

   a. **Potential Emitted substances:**

      Not necessary for these foreign facilities, because an adequate compliance certification was provided.

   b. **Controls (Air, Liquid Effluent, Solid):**

      ditto

   c. **Compliance with Federal, State and Local Emission Requirements:**

      ditto

   d. **Effect of Approval on Compliance with Current Emissions Requirements:**

      ditto

   e. **Estimated maximum yearly market volume of drug product:**

The non-confidential part of the EA gives the EIC as 1.5×10^{-4} ppb. The calculations are found on page A-6 and A-8 in the confidential part of the EA.

Fifth year domestic use is estimated as vials. Each vial contains 1.5 mL which then corresponds to liters. The substance is at 80/1000 concentration, so that corresponds to of substance.

Adequate

7. **Fate of emitted substances in the environment:**

(Ordinarily not required for an infrequent use Drug)

8. **Environmental effects of released substances:**

(Ordinarily not required for an infrequent use Drug)

9. **Use of resources and energy:**

(Ordinarily not required for an infrequent use Drug)

a. **Production:**

b. **Effect on Endangered/Threatened Species:**

Pigs are not an endangered animal and porcine lungs are in abundance.

c. **Effect on Properties Listed/Eligible for National Register of Historic Places:**

10. **Mitigation measures:**

(Ordinarily not required for an infrequent use Drug)

11. **Alternatives to the proposed action:**

(Ordinarily not required for an infrequent use Drug)

12. **List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

The name and experience of the plant managers and two consultants are given.

Adequate

13. **Certification:**

The NDA applicant must sign off for the EA.

14. **References:**

Adequate

15. **Appendices:**

The MSDS and foreign plant manager certifications are provided.

Adequate

9/24/96
Date

/S/

Prepared by
Carl J. Berninger, Ph.D.
Environmental Scientist
Center for Drug Evaluation and Research

9/24/96
Date

/S/

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

APPEARS THIS WAY
ON ORIGINAL