

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-744

MICROBIOLOGY REVIEW(S)

**REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

**Microbiologist's Review #6 of NDA 20-744
Responses to Microbiology Deficiencies
July 30, 1998**

A. 1. **APPLICATION NUMBER:** 20-744

APPLICANT: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

2. **PRODUCT NAMES:** Curosurf (poractant)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Curosurf is formulated in a suspension of 80 mg/ml. It is administered intratracheally.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Curosurf is indicated for treatment of Respiratory Distress Syndrome (RDS) in premature infants. RDS is characterized by poor lung expansion, inadequate gas exchange and gradual collapse of the lungs. Curosurf compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

B. 1. **DATE OF INITIAL SUBMISSION:** July 3, 1996

2. **AMENDMENT:** Major Amendment: March 3, 1998

3. **RELATED DOCUMENTS:**

Responses to FDA request of Information: 1/16/97, 4/25/97, 5/19/97, 7/3/98, 7/8/98, 7/16/98, 7/22/98, and 7/28/98. 1:51 p.m.
486 issued by Foreign Inspection Team (HFD-322), 3/20/98.
Responses to 486, 4/21/98.

4. **ASSIGNED FOR REVIEW:** July 6, 1998

5. **DATE OF CONSULT REQUEST:** July 6, 1998

C. REMARKS:

The submission responds to questions presented to the applicant as a result of the review of the Major Amendment dated March 3, 1998. The "List of Microbiology Deficiencies and Comments" have been copied into the "Review Notes" section of this review and the responses are individually reviewed.

D. CONCLUSIONS:

The applicant adequately responded to all deficiencies. However, the manufacturing process is extremely labor intensive, satisfactory compliance to cGMP with respect to _____ is critical to the sterility assurance of the drug product. The submission is, therefore, recommended for approval contingent on satisfactory inspection from FDA Investigator.

APPEARS THIS WAY
ON ORIGINAL

/S/

7/30/98

Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 7/30/98

cc:

NDA 20-744
HFD-570/ Div. File
HFD-805/ Uratani
HFD-570/ Toyer
HFD-570/ Nashed
drafted by: Brenda Uratani, 7/30/98
R/D initialed by P. Cooney, 7/30/98

APPEARS THIS WAY
ON ORIGINAL

MAY 29 1998

**REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

**Microbiologist's Review #5 of NDA 20-744 Major Amendment
May 29, 1998**

A. 1. APPLICATION NUMBER: 20-744

APPLICANT: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

2. PRODUCT NAMES: Curosurf (poractant)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Curosurf is formulated in a suspension of 80 mg/ml. It is administered intratracheally.

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Curosurf is indicated for treatment of Respiratory Distress Syndrome (RDS) in premature infants. RDS is characterized by poor lung expansion, inadequate gas exchange and gradual collapse of the lungs. Curosurf compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

B. 1. DATE OF INITIAL SUBMISSION: July 3, 1996

2. AMENDMENT: Major Amendment: March 3, 1998

3. RELATED DOCUMENTS:
Responses to FDA request of Information: 1/16/97, 4/25/97, and 5/19/97.
486 issued by Foreign Inspection Team (HFD-322), 3/20/98.

4. ASSIGNED FOR REVIEW: March 9, 1998

5. DATE OF CONSULT REQUEST: March 9, 1998

C. REMARKS:

The submission responds to questions presented to the applicant as a result of the Division's non-approval letter dated July 3, 1997. The CMC/Microbiology questions

D. CONCLUSIONS:

The responses to Question 3 are satisfactory. Since there is a high level of _____ in the crude Curosurf solution, the extraction by organic solvents should be performed immediately so as to prevent the risk of the drug degradation.

/S/

5/30/97

**Brenda Uratani, Ph.D.
Review Microbiologist**

/S/ 4/4/97

cc:

**NDA 20-744
HFD-570/ Div. File
HFD-805 /Uratani
HFD-570/CSO/ B. Kuzmik
HFD-570/Chemist/ Nashed
drafted by: Brenda Uratani, 5/30/97
R/D initialed by P.Cooney, 5/30/97**

**APPEARS THIS WAY
ON ORIGINAL**

**REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

**Microbiologist's Review # 3 of NDA 20-744
Response to FDA Request of Information
June 4, 1997**

A. 1. **APPLICATION NUMBER:** 20-744

APPLICANT: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

2. **PRODUCT NAMES:** Curosurf (poractant)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Curosurf is formulated in a suspension of 80 mg/ml. It is administered intratracheally.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Curosurf is indicated for treatment of Respiratory Distress Syndrome (RDS) in premature infants. RDS is characterized by poor lung expansion, inadequate gas exchange and gradual collapse of the lungs. Curosurf compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

B. 1. **DATE OF INITIAL SUBMISSION:** January 16, 1997

2. **AMENDMENT:** April 25, 1997

3. **RELATED DOCUMENTS:** NDA 20-744

4. **ASSIGNED FOR REVIEW:** May 28, 1997

5. **DATE OF CONSULT REQUEST:** May 22, 1997

C. **REMARKS:**

The submission responds to questions presented to the applicant as a result of Microbiologist's Review #1. The sponsor provides data on _____ for the manufacture of Curosurf. The validation was performed by _____

D. CONCLUSIONS:

The submitted data on _____ are satisfactory. However, maintenance of sterility _____ is a concern since there are many more manipulations between the _____ and the filling into the vials. Satisfactory inspection by FDA inspector and successful media fills are therefore crucial to ensure sterility of the final drug product.

ISI 6/4/97

Brenda Uratani, Ph.D.
Review Microbiologist

ISI
6/4/97

cc:

NDA 20-744
HFD-570/ Div. File
HFD-805 /Uratani
HFD-570/CSO/ B. Kuzmik
HFD-570/Chemist/ Nashed
drafted by: Brenda Uratani, 6/4/97
R/D initialed by P.Cooney, 6/4/97

APPEARS THIS WAY
ON ORIGINAL

MAR 20 1997

Kuzmick

**REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

**Microbiologist's Review # 2 of NDA 20-744
Response to FDA Request of Information
March 10, 1997**

A. 1. **APPLICATION NUMBER:** 20-744

APPLICANT: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

2. **PRODUCT NAMES:** Curosurf (poractant)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Curosurf is formulated in a suspension of 80 mg/ml. It is administered intratracheally.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Curosurf is indicated for treatment of Respiratory Distress Syndrome (RDS) in premature infants. RDS is characterized by poor lung expansion, inadequate gas exchange and gradual collapse of the lungs. Curosurf compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

B. 1. **DATE OF INITIAL SUBMISSION:** January 16, 1997

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:** , NDA 20-744

4. **ASSIGNED FOR REVIEW:** January 27, 1997

5. **DATE OF CONSULT REQUEST:** January 24, 1997

C. **REMARKS:**

The submission responds to questions presented to the applicant as a result of Microbiologist's Review #1. The questions from the Microbiologist's Draft of Letter to the Applicant have been copied into the "Review Notes" section of this review and the responses are individually reviewed.

MAR 20 1997

K W Z M I K

REVIEW FOR HFD-570
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

OCT 31 1996

Microbiologist's Review # 1 of NDA
October 24, 1996

A. 1. **APPLICATION NUMBER:** 20-744

APPLICANT: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

2. **PRODUCT NAMES:** Curosurf (poractant)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Curosurf is formulated in a suspension of 80 mg/ml. It is administered intratracheally.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Curosurf is indicated for treatment of Respiratory Distress Syndrome (RDS) in premature infants. RDS is characterized by poor lung expansion, inadequate gas exchange and gradual collapse of the lungs. Curosurf compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

B. 1. **DATE OF INITIAL SUBMISSION:** July 3, 1996

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:**

4. **ASSIGNED FOR REVIEW:** July 16, 1996

5. **DATE OF CONSULT REQUEST:** July 9, 1996

C. **REMARKS:**

Curosurf suspension is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a porcine lung extract consisting of 99% polar lipids (mainly phospholipids) and about 1% hydrophobic low MW proteins (surfactant associated proteins, SP B and SP-C). It is suspended in 0.9% NaCl solution, resulting in a suspension containing 80 mg/ml of surfactant and 1 mg/ml of protein. It contains no preservatives.