CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-744

CHEMISTRY REVIEW(S)

Dunn

OCT 2 2 1999

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA # 20-744 **CHEM. REVIEW # 3** **REVIEW DATE** Oct 20, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT [BZ]	09-AUG-96	13-AUG-96	15-AUG-96
AMENDMENT [BZ]	16-AUG-96	16-AUG-96	19-AUG-96
AMENDMENT [BZ]	29-AUG-96	30-AUG-96	03-SEP-96
AMENDMENT [BZ]	30-AUG-96	03-SEP-96	04-SEP-96
AMENDMENT [BC]	01-NOV-96	12-NOV-96	12-NOV-96
AMENDMENT [BC]	08-NOV-96	12-NOV-96	12-NOV-96
AMENDMENT [BC]	05-DEC-96	06-DEC-96	09-DEC-96
AMENDMENT [BZ]	10-DEC-96	11-DEC-96	12-DEC-96
AMENDMENT [BZ]	16-JAN-97	17-JAN-97	22-JAN-97
AMENDMENT [BZ]	26-FEB-97	27-FEB-97	28-FEB-97
AMENDMENT [BC]	25-APR-97	28-APR-97	30-APR-97
AMENDMENT [BC]	19-MAY-97	20-MAY-97	28-MAY-97
AMENDMENT [BZ]	19-MAY-97	21-MAY-97	28-MAY-97
AMENDMENT [BC]	08-SEP-97	11-SEP-97	18-SEP-97
AMENDMENT [BC]	22-DEC-97	12-JAN-98	14-JAN-98
AMENDMENT [AZ]	03-MAR-98	04-MAR-98	12-MAR-98
AMENDMENT [BC]	19-MAR-98	23-MAR-98	06-APR-98
AMENDMENT [BC]	23-JUN-98	24-JUN-98	30-JUN-98
AMENDMENT [BC]	02-JUL-98 ✓	xx-JUL-98	06-JUL-98
AMENDMENT [BC]	13-JUL-98	14-JUL-98	14-JUL-98
AMENDMENT [BC]*	18-Nov-98	19-Nov-98	22-Nov-98
AMENDMENT [AC]*	14-May-99	19-May-99	28-May-99
AMENDMENT [BZ]*	07-Jul-99	08-Jul-99	17-Sep-99
AMENDMENT [BC]*	15-Jul-99	16-Jul-99	22-Jul-99
AMENDMENT [BL]*	16-Aug-99	18-Aug-99	17-Sep-99
AMENDMENT [BC]*	06-Oct-99	07-Oct-99	18-Oct-99
AMENDMENT [BC]*	15-Oct-99	18-Oct-99	18-Oct-99
AMENDMENT [BC]*	19-Oct-99	20-Oct-99	20-Oct-99

* Subject of this review

NAME & ADDRESS OF APPLICANT:

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, California 94558

DRUG PRODUCT NAME

Proprietary: **CUROSURF® Intratracheal Suspension**

Nonproprietary/USAN: **poractant alfa** (USAN letter dated 4/29/98)

BAN: Poractant alpha.

Code Name/#: CAS Reg. Nr.: 129069-19-8.

Chem.Type/Ther.Class: 1S/601

PHARMACOL. CATEGORY/INDICATION: Lung surfactant replacement for treatment of Respiratory Distress Syndrome (RDS) in premature infants.

DOSAGE FORM: Sterile liquid suspension containing 80 mg/mL of surfactant mixture suspended in 0.9 % NaCl solution.
No preservatives. Kept refrigerated. *Recommended Dose*: 1.5 mL/kg birth weight. Supplied in single-use glass vials containing either 1.5 mL (120 mg ± 12 mg of surfactant) or 3 mL (240 ± 24 mg of surfactant) of Curosurf Intratracheal Suspension.

STRENGTHS: Complex mixture of phospholipids and hydrophobic proteins extracted from porcine lungs. It contains 80±10 mg/mL of solids. Approximate concentration of phosphatidylcholine (PC) is 55 mg/mL (of total phosphorus) and approximate concentration of dipalmitoylphosphatidylcholine (DPPC), which is a sub-fraction of PC, is 31 mg/mL (of total phosphorus). Total protein fraction is 0.9 mg/mL (0.5-1.4 mg/mL) which corresponds to and content of SP-B is about 0.2 mg/mL (0.2-0.4 mg/mL) which corresponds to

ROUTE OF ADMINISTRATION: Intratracheal instillation *via* endotracheal tube.

DISPENSED: _X_ Rx ___ OTC

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

Complex mixture of phospholipids and hydrophobic proteins. For structures see Chem. Review #1 dated 20-May-97.

SUPPORTIVE DOCUMENTS:

DMF Number	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1
		Rubber Closure (design, rubber formulation, technical data and specifications) manufactured by	Adequate	14-Aug-95 & 12-Feb-96	p. 80-81

RELATED DOCUMENTS:

Pending. Request for validation of the analytical methods will be submitted shortly.

REMARKS:

This is CMC review of a major amendment dated 14-May-99 and several minor amendments as listed on the first page of this review. Overall EER status is ACCEPTABLE as of Sep 7, 1999. Comments, if any, resulting from Pharm/Tox – Statistical evaluation of applicant's response to item number 12 should be included in the letter. MV package should be on file (to arrive by Nov 8, 1999) before issuing action letter.

CONCLUSIONS & RECOMMENDATIONS:

The application is recommended for APPROVAL with Phase 4 commitments from the CMC standpoint.

/S/

Eugenia M. Nashed, Ph.D., Review Chemist

cc:
Org. NDA 20-744
HFD-570/Division File
HFD-570/ENashed
HFD-570/KDunn
HFD-570/GPoochikian
HFD-570/DBirenbaum
HFD-570/JSun

R/D Init by: /S/ 9/24/99

APPEARS THIS WAY
ON ORIGINAL

TOY#2

JUL 14 1998

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA # 20-744 **CHEM. REVIEW # 2** **REVIEW DATE** July 13, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT [BZ]	09-AUG-96	13-AUG-96	15-AUG-96
AMENDMENT [BZ]	16-AUG-96	16-AUG-96	19-AUG-96
AMENDMENT [BZ]	29-AUG-96	30-AUG-96	03-SEP-96
AMENDMENT [BZ]	30-AUG-96	03-SEP-96	04-SEP-96
AMENDMENT [BC]	01-NOV-96	12-NOV-96	12-NOV-96
AMENDMENT [BC]	08-NOV-96	12-NOV-96	12-NOV-96
AMENDMENT [BC]	05-DEC-96	06-DEC-96	09-DEC-96
AMENDMENT [BZ]	10-DEC-96	11-DEC-96	12-DEC-96
AMENDMENT [BZ]	16-JAN-97	17-JAN-97	22-JAN-97
AMENDMENT [BZ]	26-FEB-97	27-FEB-97	28-FEB-97
AMENDMENT [BC]*	25-APR-97	28-APR-97	30-APR-97
AMENDMENT [BC]*	19-MAY-97	20-MAY-97	28-MAY-97
AMENDMENT [BZ]*	19-MAY-97	21-MAY-97	28-MAY-97
AMENDMENT [BC]*	08-SEP-97	11-SEP-97	
AMENDMENT [BC]*	22-DEC-97	12-JAN-98	14-JAN-98
AMENDMENT [AZ]*	03-MAR-98	04-MAR-98	12-MAR-98
AMENDMENT [BC]*	19-MAR-98	23-MAR-98	06-APR-98
AMENDMENT [BC]*	23-JUN-98	24-JUN-98	30-JUN-98
AMENDMENT [BC]*	02-JUL-98	xx-JUL-98	06-JUL-98
AMENDMENT [BC]*	02-JUL-98	xx-JUL-98	06-JUL-98

* Subject of this review

NAME & ADDRESS OF APPLICANT: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, California 94558

DRUG PRODUCT NAME

Proprietary: **CUROSURF® Intratracheal Suspension**

Nonproprietary/USAN: **poractant** (no response from USAN available yet)
BAN: Poractant alpha.

Code Name/#: CAS Reg. Nr.: 129069-19-8.

Chem.Type/Ther.Class: 1S/601

PHARMACOL. CATEGORY/INDICATION: Lung surfactant replacement for treatment of Respiratory Distress Syndrome (RDS) in premature infants.

DOSAGE FORM: Sterile liquid suspension containing 80 mg/mL of surfactant suspended in 0.9 % NaCl solution.

No preservatives. Kept refrigerated. *Recommended Dose*: 1.5 mL/kg birth weight. Supplied in single-use glass vials containing either 1.5 mL (120 mg of surfactant) or 3 mL (240 mg of surfactant) of Curosurf Intratracheal Suspension.

STRENGTHS: Complex mixture of phospholipids and hydrophobic proteins extracted from porcine lungs. It contains 80±10 mg/mL of solids. Approximate concentration of phosphatidylcholine (PC) is 52 mg/mL (of total phosphorus) and dipalmitoyl-phosphatidylcholine (DPPC) which is a subfraction of PC has approximate concentration of 31 mg/mL (of total phosphorus). Total protein fraction is (0.4 -1.6 mg/mL) and content of SP-B is 0.1-0.4 mg/mL.

ROUTE OF ADMINISTRATION: Intratracheal instillation *via* endotracheal tube.

DISPENSED: _X_ Rx ___ OTC

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

Complex mixture of phospholipids and hydrophobic proteins. For structures see Chem. Review #1.

SUPPORTIVE DOCUMENTS:

DMF Number	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1
		Rubber Closure (design, rubber formulation, technical data and specifications) manufactured by	Adequate	14-Aug-95 & 12-Feb-96	p. 80-81

RELATED DOCUMENTS:

IND Curosurf (since 04-May-93); Sponsor: Dey Labs.

OTHER APPROVED LUNG SURFACTANTS:

- NDA 20-032, Survanta, Bovine Lung Extract (minced lungs).
- NDA 20-044, Exosurf, mixture of DPPC, Cetyl Alcohol and Tyloxapol (synthetic).
- NDA 20-521, Infasurf, Calf Lung Extract (lavage).

CONSULTS:

Nomenclature:

Consult to evaluate the trade name "Curosurf" was requested on 3-Jul-96.
Received response #644 (NO OBJECTION) from CDER Labeling and Nomenclature Committee. Request for assigning of the established name (poractant) is pending with USAN.

EER:

Inspection was carried in March 1998 at three manufacturing and testing sites in Investigator issued forms 483 for all three sites. AC status is available for the drug substance manufacturing and testing site and NA is recommended for the drug product manufacturing and testing sites. Currently, the OC is recommending overall WITHHOLD (see Review Notes for details).

EA:

Consult request submitted to Nancy Sager 29-Aug-96 and response dated 24-Sep-96 received. One deficiency was forwarded to the applicant in letter dated 19-Nov-96. Response from the applicant with a consult request dated 24-Jan-97 was forwarded for review. EA evaluation: ADEQUATE. FONSI dated 4-Feb-97 on file.

Microbiology:

Consult requested on 30-Jul-96. Review dated 31-Oct-96 received and deficiencies forwarded to applicant in letter dated 19-Nov-96. Response from the applicant with a consult request dated 24-Jan-97 was forwarded to microbiologist. Preliminary microbiology comments were forwarded to the applicant during teleconference on March 5, 1997. Applicant's response dated March 3, 1998 was reviewed by microbiologist. Microbiology review dated 29-May-98 resulted in comments which were faxed to the applicant on June 18, 1998. Response from applicant dated 2-Jul-98 was reviewed by microbiologist and resulted in APPROVABLE status providing that adequate data on the media fill for the first part of the drug product manufacturing process is provided. Applicant provided commitment to submit data by the end of July 1998. Microbiologist is planning to complete her review by August 4-5, 1998.

MV :

Request for validation of the analytical methods will be submitted upon satisfactory response to CMC comments.

REMARKS:

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-744 CHEM. REVIEW # 1 REVIEW DATE: 5/20/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA*	03-JUL-96	03-JUL-96	22-JUL-96
AMENDMENT [BZ]*	09-AUG-96	13-AUG-96	15-AUG-96
AMENDMENT [BZ]*	16-AUG-96	16-AUG-96	19-AUG-96
AMENDMENT [BZ]*	29-AUG-96	30-AUG-96	03-SEP-96
AMENDMENT [BZ]*	30-AUG-96	03-SEP-96	04-SEP-96
AMENDMENT [BC]*	01-NOV-96	12-NOV-96	12-NOV-96
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AMENDMENT [BZ]*	10-DEC-96	11-DEC-96	12-DEC-96
AMENDMENT [BZ]*	16-JAN-97	17-JAN-97	22-JAN-97
AMENDMENT [BZ]*	26-FEB-97	27-FEB-97	28-FEB-97

* Subject of this review

NAME & ADDRESS OF APPLICANT: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, California 94558

DRUG PRODUCT NAME

Proprietary: CUROSURF®

Nonproprietary/USAN: poractant (applied for; not assigned by USAN yet).
BAN: Poractant alpha. CAS Reg. Nr.: 129069-19-8.

Code Name/#:

Chem.Type/Ther.Class: 1S/601

PHARMACOL. CATEGORY/INDICATION: Lung surfactant replacement for treatment of Respiratory Distress Syndrome (RDS) in premature infants.

DOSAGE FORM: Sterile liquid suspension containing 80 mg/mL of surfactant suspended in 0.9 % NaCl solution. No preservatives. Kept refrigerated. Recommended Dose: 1.5 mL/kg birth weight. Supplied in single-use glass vials containing either 1.5 mL (120 mg of surfactant) or 3 mL (240 mg of surfactant).

STRENGTHS: Complicated mixture of phospholipids and hydrophobic proteins extracted from porcine lung surfactant. It contains 80±10 mg/mL of solids. Approximate concentration of phosphatidylcholine (PC) is of total phosphorus (mg/mL and dipalmitoylphosphatidylcholine (DPPC)

of total phosphorus . Total protein: (*ca.* 0.4 -1.6 mg/mL; no specification. for SP-B or SP-C established yet).

ROUTE OF ADMINISTRATION: Intratracheal instillation *via* endotracheal tube.

DISPENSED: _X_ Rx ___ OTC

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

Complicated mixture of phospholipids and hydrophobic proteins. For structures see Review Notes.

SUPPORTIVE DOCUMENTS:

DMF Number	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1
		Rubber Closure (design, rubber formulation, technical data and specifications) manufactured by	Adequate	14-Aug-95 & 12-Feb-96	p. 80-81

RELATED DOCUMENTS:

IND Curosurf (since 04-May-93); Sponsor: Dey Labs.

CONSULTS:

Nomenclature:

Consult to evaluate the trade name "Curosurf" was requested on 3-Jul-96.
Received response #644 (NO OBJECTION) from CDER Labeling and Nomenclature Committee.
Request information about the status of applicant's application for assigning the established name (poractant) was placed with USAN.

EERs:

Submitted on 22-Jan-97, after receiving requested information from applicant. Site at which is involved in the drug product manufacture and testing for sterility is currently under re-construction. Information was forwarded to the Field Investigator. The construction progress and possible inspection problems associated with it were discussed with the applicant during teleconference on 5-Mar-97. All sites were made available for the inspection to take place on May 26 - June 13, 1994. However, due to the un-finished construction/validation process at the site, the establishment is considered not ready for inspection. UNACCEPTABLE.

EA:

Consult request submitted to Nancy Sager 29-Aug-96 and response dated 24-Sep-96 received. One deficiency was forwarded to the applicant in letter dated 19-Nov-96. Response from the applicant with a consult request dated 24-Jan-97 was forwarded for review. EA evaluation dated Feb-97: ADEQUATE. FONSI dated 4-Feb-97 on file.

Microbiology:

Consult requested on 30-Jul-96. Review dated 31-Oct-96 received and deficiencies forwarded to applicant in letter dated 19-Nov-96. Response from the applicant with a consult request dated 24-Jan-97 was forwarded to microbiologist. Preliminary microbiology comments were forwarded to the applicant during teleconference on 5-Mar-97. Microbiology Review #2 dated 10-Mar-97 was received with note: "not recommended for approval as submitted". DEFICIENT.

MV :

Request for methods' validation will be submitted upon satisfactory response to CMC comments about methods.

REMARKS:

This is an initial chemist's review of the original NDA application #20-744 dated 3-Jul-96 and filed on 28-Aug-96, after teleconference with applicant on 31-Jul-96 and after review of CMC amendments dated 9-Aug-96 and 16-Aug-96 (pre-NDA meeting with Dey Labs and Chiesi was held on 31-Oct-95). Microbiology comments were forwarded to the applicant in 19-Nov-96 IR letter. Preliminary CMC comments and preliminary microbiology comments to applicant's response (16-Jan-97) were forwarded to the applicant during 5-Mar-97 teleconference. All outstanding CMC and microbiology deficiencies are listed in the Chemist's Draft Letter. For other remarks see the Review Notes (p. 4).

CONCLUSIONS & RECOMMENDATIONS:

The application is not recommended for approval before the outstanding microbiology and chemistry issues are adequately addressed and before acceptable EER is available. All outstanding CMC and microbiology deficiencies are listed in the Chemist's Draft Letter. The above should be communicated to the Applicant as soon as possible.

cc:
Org. NDA 20-744
HFD-570/Division File
HFD-570/ENashed
HFD-570/BKuzmik
HFD-570/GPoochikian
HFD-570/MPina/BGillespie/JSun
HFD-160/BUratani [HFD-805]
R/D Init by /S/ 5/20/97

/S/
Eugenia M. Nashed, Ph.D. Review Chemist