

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-744

ADMINISTRATIVE DOCUMENTS

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Robertson et al.

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[54] **NATURAL PULMONARY SURFACTANT,
METHOD OF PREPARATION AND
PHARMACEUTICAL COMPOSITIONS**

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Italy

[21] **Appl. No.:** 177,771

[22] **Filed:** Apr. 5, 1988

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.** _____ A61K 37/22; A61K 31/685

[52] **U.S. Cl.** _____ 514/21; 424/557;
514/2; 514/78; 514/975; 520/350; 520/359

[58] **Field of Search** _____ 514/2, 21, 78, 975;
530/350, 359, 417; 424/95, 557

[56] **References Cited**

U.S. PATENT DOCUMENTS

4312360 1/1982 Clements _____ 514/78

4338301 7/1982 Tessaro et al. _____ 424/95

4397839 8/1983 Tanaka _____ 424/95

4603124 7/1986 Takei et al. _____ 514/2 X

4765987 8/1988 Bonte et al. _____ 514/78 X

FOREIGN PATENT DOCUMENTS

8706943 11/1987 PCT Int'l Appl. _____ 514/2

Primary Examiner—Howard E. Schain

Attorney, Agent, or Firm—Bocknam and Archer

[57] **ABSTRACT**

A pulmonary surfactant of animal origin made up of a high percentage of phospholipids (~99%), by a protein fraction and characterized by the absence of carbohydrates and cholesterol.

The surfactant of the invention, obtained through filtration, centrifugation and extraction and by chromatography in inverse phase, allows better therapeutic results in the treatment of infant and adult respiratory distress syndromes (IRDS and ARDS).

4 Claims, No Drawings

APPEARS THIS WAY
ON ORIGINAL

NATURAL PULMONARY SURFACTANT, METHOD OF PREPARATION AND PHARMACEUTICAL COMPOSITIONS

Subject of the invention is a pulmonary surfactant (PS) preparation of animal origin, with a low toxicity and optimal surface characteristics, for use in the prevention and therapy of IRDS (Infant Respiratory Distress Syndrome) and ARDS (Adult Respiratory Distress Syndrome) related to HMD (Hyaline Membrane Disease).

Normal pulmonary functionality depends on the presence of a particular material, the pulmonary surfactant, which is in charge of stabilizing the alveoli by reducing surface tension, in particular during the expiration phase.

The presence of pulmonary surfactant is of particular importance at the moment of birth.

Lack of PS is a key factor in the pathogenesis of IRDS, a disease which affects 10-15% of premature newborn babies. These subjects require artificial ventilation with high oxygen concentration and high insufflation pressure. IRDS death rate is around 25% and several of the survivors are left with chronic pulmonary complications mainly due to the prolonged artificial ventilation, and with secondary neurologic disfunctions due to cerebral hypoxia damage.

Lack of pulmonary surfactant is an important factor also in ARDS. This pathology can develop in cases of multiple trauma, aspiration, pancreatitis, etc. with a 40-70% death rate.

Administration of supporting doses of the lacking surfactant has proved useful in the treatment of these pathologies.

The pulmonary surfactants known to the art belong to three fundamental groups:

1. ARTIFICIAL PULMONARY SURFACTANT

Preparations of artificial surfactants with a base of dipalmitoylphosphocholine or of phospholipid mixtures in variable concentrations and ratios, optionally coupled with components such as sugars, aminoacids, alcohols or fat acids have been described in several patents: DE 2900300 (Klitzing LV); JP 58222022 (Teijin KK); EP 110498; U.S. Pat. No. 4312860 (University of California); DE 3229179 (Natterman A & Cie GmbH); JP 61065821 (Tokyo Tanabe KK).

At clinical-pharmacological level, however, the artificial surfactant did not prove to be very effective.

2. HUMAN PULMONARY SURFACTANT

Derived by extraction from amniotic liquid.

Although effective, it has proved to be of little practical utility, both for its high protein contents (which can lead to sensitization of the treated subject) and for difficulties of preparation on a large scale, as to obtain a dose an amniotic-liquid-taking from three terminal pregnancies is necessary. It also presents a high risk of viral contamination with possible transmission of pathologies as serious as AIDS.

3. NATURAL PULMONARY SURFACTANT

Extracted from mammal lung and with an effectiveness comparable to the human surfactant, it presents the great advantage of simplicity in preparation and a lower protein contents.

Pulmonary surfactants of natural origin of animal extraction have been prepared before. For instance, DE 3021006, JP 58045299 and EP 119056 (Tokyo Tanabe KK), describe a rather complex method which, through a series of operations such as repeated centrifugations (850×g to 20,000×g), lyophilization and various extractions, leads to a natural PS containing, besides phospholipids (75-95.5%) and proteins (0.5-5%), also carbohydrates (0.1-2%), neutral lipids (0.3-14%) and total cholesterol (0-8%), components of no use to the pharmacological action.

Also the surfactant prepared according to EP 145003 (Veb Arzneimittel Dresden) contains, in an even higher percentage (3-40%), an apolar lipid fraction, of no use to the biological activity and has instead low contents (40-70%) of phospholipids which represent on the contrary the most important physiological component.

Finally EP 55041, JP 58183620, JP 58183621, JP 58164513 (Teijin KK) describe natural, artificial or semi-natural (i.e. added with synthetic phospholipids) surfactants totally de-proteinized. And the most recent studies have yet attributed to the presence of proteins a considerable functional meaning.

After long and profound studies, started several years ago, applicant has prepared a new pulmonary surfactant, subject of the present invention, whose composition is optimum for a balanced pharmacological activity.

A preparation process of this surfactant has also been worked out which, through the use of animal lung, allows to attain with few operations separation of the required fraction.

A first aspect of the invention refers therefore to an animal pulmonary surfactant presenting the following characteristics:

(a) the highest polar lipids concentration (99%), mainly phospholipids, as regards to other preparations;

(b) total absence both of free carbohydrates, cholesterol, triglycerides and cholesterol esters, components of no use for surface activity (Suzuki Y., J. Lipid Res. 23, 62-69, 1982) and of other neutral lipids ineffective from the pharmacological point of view (Nohara K., Eur. J. Resp. Dis. 69, 321-335, 1986);

(c) the presence of a protein component, characterized by a particularly high presence of hydrophobic amino acids, whose maximum concentration is lower than 1-1.5%. The proteic part is made up exclusively of hydrophobic proteins of molecular weight ranging from 3 to 4 K (K=kilodaltons), which are important for absorption of the phospholipids at the air-liquid interface level.

A second aspect of the invention refers to a preparation method which through a simple process, reproducible and feasible on industrial scale, allows to obtain a surfactant of the indicated characteristic.

Triturated animal lungs are washed in a physiological solution. They are filtered and centrifuged at speeds between 1,000 and 5,000×g for a time of one to three hours, according to the speed.

Extraction of the surfactant is then carried out with an organic solvent, preferably made up of a 1:2 methyl alcohol/chloroform mixture. The organic phase is water-washed and evaporated, thus obtaining a raw lipid fraction which is recovered with organic solvent, preferably formed by a 1:2-dichloroethane/dichloromethane mixture in a 1:4 ratio. Subsequently, by gel chromatography, the polar lipid component, made of phos-

3 phospholipids, is separated from the apolar one, made up of triglycerides, cholesterol and cholesterol esters.

The phospholipid fraction, the one for clinical use, is sterilized by ultrafiltration and stored at a temperature of at least -20°C . In the alternative, it can be lyophilized and stored at -20°C .

The preparation of the surfactant subject of the present invention is exemplified in detail hereinafter, without limiting it in any way.

EXAMPLE 1

Pig lungs are triturated in a mixer and the tissue fragments are washed in a physiological solution. The mixture is filtered and subjected to preliminary centrifugation at $1,000\times g$ at 20°C . for 15 min., to eliminate cellular fragments. The supernatant liquor is then re-centrifuged at $3,00\times g$ at 4°C . for 2 hours.

The raw (solid) surfactant is removed and extracted with 2:1 chloroform/methyl alcohol (V/V), filtered, washed with water and the organic phase is evaporated thus obtaining a raw lipid extract. The lipid fraction extract (1-1.5 g) is recovered with 20 ml of 1:4 1,2-dichloroethane/methyl alcohol mixture (V/V) and separated by chromatography in reverse phase on LIPI-DEX -5000 (4×21.5 cm; Packard Instruments Co.) column with a 1,2-dichloroethane/methyl alcohol 1:4 (V/V) eluant and a flow of 60-90 ml/h. Fraction 1 (0-270 ml) contains only phospholipids, fraction 2 (270-405 ml) contains few phospholipids and other polar lipids, while the apolar lipids (triglycerides, cholesterol and its esters) are kept by the column.

Fraction 1 can be used as such.

It is possible to recover the phospholipids contained in fraction 2 by proceeding as follows. Fraction 2 is re-chromatographed on the same column and the first fraction which is obtained (0-270 ml) is joined to the fraction 1 of the previous chromatography. The two joined fractions are dried (at temperatures lower than 40°C), dissolved in 98:2 chloroform/methyl alcohol (V/V), sterilized by filtration (prefilter $0.45\ \mu\text{m}$ and filter $0.2\ \mu\text{m}$, and stored in a freezer at -20°C .

EXAMPLE 2

The phospholipid fraction obtained with the method described in example 1 is defrosted, always under sterilization, dried and re-suspended in a physiological solution by means of ultrasounds at a suitable frequency, i.e. 45-50 kilohertz, with energy at 50 Watts. This is a rather critical step in the process of obtaining an active product, as it has been experimentally verified in certain cases that even mild variations of the sonic frequency, while leaving unaltered the product's chemical and chemico-physical characteristics, may considerably influence the biological activity.

The suspension thus obtained is distributed in vials for subsequent therapeutic use in a concentration of 80 mg of phospholipids/ml of salt solution.

With the method described in Examples 1 and 2 it is possible to isolate from the lungs of an adult pig about 200 mg of pulmonary surfactant, approximately the contents of a dose of product for the treatment of IRDS. Higher doses are required for treatment of ARDS.

For each batch of product, evaluation of the phospholipids concentration and composition, and of the quantity of the other components was carried out each time. Protein contents were evaluated through analysis of the amino acids.

4 Table I illustrates the composition of a phospholipid fraction of a preparation obtained according to the method described in Example 1.

Phospholipids	mol %
Phosphatidylcholine	75.1 ± 3.3
Phosphatidylethanolamine	7.5 ± 2.7
Phosphatidylserine	1.2 ± 1.1
Phosphatidylinositol	7.2 ± 1.7
Phosphatidylglycerol	3.5 ± 1.3
Lysophosphatidylcholine	0.7 ± 0.5
Sphingomyelin	4.7 ± 1.7

In the description which follows, in the aim to simplify, reference is made to the phospholipid fraction only as the essential and predominant component of the therapeutic product.

The surface properties of each batch have also been evaluated at 37°C . with the pulsating bubble technique (Surfactometer International, Toronto, Canada) (Enhorning G., *J. Appl. Physiol.* 43, 198-203, 1977).

At a concentration of 10 mg/ml the preparation presents a minimum of surface tension $<5\ \text{mN/m}$ at 50% of surface compression in 5 min pulsation.

The sterility of the preparation was confirmed by the bacteriological analysis.

The effectiveness of this preparation was tested on animals, in cases both of spontaneous IRDS in premature newborn rabbits and of ARDS induced in guinea pigs through repeated pulmonary wash.

Tests on animals

For these tests (carried out according to the method described by Lachmann B. et al. *Pediatr. Res.*, 15, 833-838, 1981) rabbits, prematurely born by Caesarian section on the 27th day of pregnancy, immediately tracheotomized and intubated, were used.

Eleven of these rabbits were treated by administering, through the cannula, pulmonary surfactant prepared as described in the present invention, while 15 others did not receive anything and made up the control group.

All the animals, the treated and the control ones, were parallelly connected with an artificial respirator, kept under artificial ventilation at constant pressure, with 100% oxygen, at 40 actions/min and subjected to a standardized sequence of insufflation pressure. The lungs were in fact first expanded by ventilating for 1 min at a pressure of 35 cm of H_2O . Pressure was then gradually lowered at different times down to 15 cm of H_2O . Finally it was again increased for 5 min up to 25 cm of H_2O . Tidal volume was measured every 5 min.

The results are shown in Table II.

Time (min)	P_f (cm H_2O)	TV (treated) (ml/kg)	TV (control) (ml/kg)
5	25	34.5	2.2
10	25	34.0	2.0
15	25	34.5	2.2
20	20	15.0	1.3
25	15	8.1	1.0
30	25	40.0	3.0

A remarkable increase of the tidal volume was observed in the treated animals in comparison to the control ones.

Histologic analysis of paraffin lung sections, stained with hematoxylin and eosin examined microscopically,

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showed a remarkable increase of the volume of the alveolar compartment in the treated group.

Similar results were obtained by administering the surfactant, subject of the present invention, to guinea pigs with a respiratory insufficiency induced according to the method described by Berggren P. et al., *Acta Anesthesiol. Scand.* 30, 321-328, 1986.

In the treated cases, as shown in Table III, there is a quicker return to normal values of gas exchange in comparison to the control cases.

Time (min)	Treated		Control	
	paO ₂ (Kpa)	PaCO ₂ (Kpa)	paO ₂ (Kpa)	PaCO ₂ (Kpa)
0*	7.5	8.3	8.0	6.8
15	47	5.9	9.0	7.0
30	48	5.5	10.0	7.2
45	50	5.3	10.1	7.0
60	55	5.0	10.3	6.9

* Time of instillation of a dose of PS in the treated animals.

Clinical Tests

Clinical surveys were carried out in specialized centres for premature newborn babies with Hyaline Membrane Disease, who revealed great respiratory insufficiency and, in spite of intermittent mechanical ventilation at positive pressure with oxygen percentage higher than 60%, presented hypoxia, hypercapnia and acidosis.

The results obtained in a controlled study, carried out on a group of 10 newborn babies, 5 treated with the invention's surfactant and 5 controls treated with conventional therapy, are reported hereinafter.

At the moment of treatment the patients were disconnected from the respirator and the surfactant was injected into the endotracheal tube at a dose of 2.5 ml/kg. equal to 200 mg of phospholipids/kg.

After administration the babies were ventilated manually with bubble for 1 min at a frequency of 40-60 actions/min and with the same gas mixture used previously.

The patients were then reconnected to the respirator set as previously; subsequent variations were made in accordance with clinical response and modification in the blood gases.

The babies making up the control group were also disconnected from the ventilator and ventilated manually for 2 min at the same conditions used for the patients treated with the surfactant.

The effectiveness of the treatment was documented by the movement of the various indexes on respiratory functionality.

In particular within about 5 min, paO₂ (Partial Arterial Oxygen Pressure) values were undergoing a rapid and dramatic increase so that the pa/AO₂ ratio (ratio between partial oxygen pressures at arterial level and at alveolar level) reached at 15 min a median value three times higher than the initial one (30.6 against 10.4; p<0.001), stabilizing then, after a slight decrease between the first and second hour, on values approx. double in comparison to the starting ones.

In the control group instead, the pa/AO₂ ratio did not show any notable change in the initial median value of 7.62.

Also the pulmonary radiologic findings documented improvement of the pathology in the treated subjects with a decrease in parenchymal fluid retention and in distension of bronchioli.

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The radiologic findings on the babies of the control group instead did not reveal any significant change in the first 48-72 hours of observation.

It is important to point out finally that in the cases treated with the invention's pulmonary surfactant a significant reduction in the time of treatment with artificial ventilation at positive pressure and in the duration of the oxygen therapy was observed.

This allowed a reduction both in the duration of the intensive therapy, highly expensive, and of the risks connected to invasive treatments. Several authors in fact reckon that the pulmonary damage consequent to IRDS is linked also to the resuscitation therapy and in particular to the prolonged exposure to high oxygen concentrations.

Moreover, there was no evidence of immunological complications in the surviving patients, which confirms the low antigenicity of the surfactant of the invention.

The use of exogenous surfactant acquires therefore a considerable importance both in prevention and therapy of respiratory disease syndromes.

For the foreseen therapeutic use, phospholipid suspensions in physiologic solution of 80 mg/ml concentration, instilled in doses of 2.5 ml/kg equal to about 200 mg of phospholipids/kg of body weight, have proved to be particularly suitable.

The treatment is normally carried out by direct endotracheal instillation of the suspension. Another possibility is administration by nebulization.

We claim:

1. An animal pulmonary surfactant which consists of polar lipids and proteins wherein the polar lipids are mainly phospholipids and the proteins are hydrophobic low molecular weight proteins of 3-14 KD (Kilodaltons), the polar lipid content is 98.5-99%, the protein content is less than 1.5%, and the phospholipid fraction contains at least 70-75% by weight of phosphatidylcholine, 40-45% of which consists of dipalmitoylphosphatidylcholine, said surfactant is free of carbohydrates, cholesterol, triglycerides and cholesterol esters.

2. A process of preparation of a pulmonary surfactant which consists of an animal pulmonary surfactant consisting of polar lipids and proteins wherein the polar lipids are mainly phospholipids and the proteins are hydrophobic low molecular weight proteins of 3-14 KD (Kilodaltons), the polar lipid content is 98.5%-99%, the protein content is less than 1.5%, the phospholipid fraction contains at least 70-74% by weight of phosphatidylcholine, 40-45% of which consists of dipalmitoylphosphatidylcholine, and is free of carbohydrates, cholesterol, triglycerides and cholesterol esters, which comprises the steps of:

- trituration animal lungs to obtain triturated lungs;
- washing said triturated lungs in a salt solution and filtering off the filtrates to obtain a solid fraction;
- centrifuging the solid fraction;
- extracting with an organic solvent;
- evaporating the solvent and
- recovering the polar components by gel chromatography.

3. The process according to claim 2, wherein step (f) is carried out by chromatography in inverse phase on LIPIDEX -5000® column, with a 1,2-dichloroethane/methanol 1:4 (V/V).

4. A pharmaceutical composition for the cure of Infant Respiratory Distress Syndrome in premature infants and Adult Respiratory Distress Syndrome, in a suspension in vials for inhalation or endotracheal administration containing as active principle a pulmonary surfactant according to claim 1, the surfactant being suspended in physiological solution of concentration between 50 and 100 mg of phospholipids/ml.

EXCLUSIVITY SUMMARY FOR NDA # 20-744 SUPPL # _____

Trade Name Curosurf Generic Name poractant alpha

Applicant Name DEY HFD # 570

Approval Date If Known November 17, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES NO

b) Is it an effectiveness supplement?
YES NO

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

___NO_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

APPEARS THIS WAY
ON ORIGINAL

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

APPEARS THIS WAY
ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

APPEARS THIS WAY

ON ORIGINAL

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

APPEARS THIS WAY
ON ORIGINAL

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ____ YES /___/ ! NO /___/ Explain: _____

!
!

Investigation #2 !

IND # ____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

!

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / /

NO / /

If yes, explain: _____

ISI

10/27/99

Signature

Date

Title: Project Manager

APPEARS THIS WAY
ON ORIGINAL

ISI

11/17/99

Signature of [redacted]
Division Director

Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20744</u>	Trade Name:	<u>CUROSURF (PORACTANT) SUSPENSION 80MG/ML</u>
Supplement Number:		Generic Name:	<u>PORACTANT</u>
Supplement Type:		Dosage Form:	<u>Suspension; Intratracheal</u>
Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>treatment (rescue) of RDS</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Adequate for SOME pediatric age groups
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

8/10/98 This product is only indicated for neonates. There is no need for this product in other pediatric age groups.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, KEARY DUNN

/s/

Signature

 11/16/99

Date

APPEARS THIS WAY
ON ORIGINAL

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-744

Trade (generic) names CURDSURF

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&W studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

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Page 2 -- Drug Studies in Pediatric Patients

5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

*CURASURF is indicated for treatment (rescue) of
Respiratory Distress Syndrome (RDS) in premature infants*

APPEAR THIS WAY

/S/

Signature of Preparer

5/20/97

Date

cc: Orig NDA
HFD-570/Div File
NDA Action Package



DEY LABORATORIES
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-0791

July 3, 1996

**Certification Pursuant to Section 306(k)(1)
of the Food Drug and Cosmetic Act
[21 U.S.C. 335a (k)(1)]**

It is hereby certified that Dey Laboratories did not use in any capacity to services of any person debarred under subsection (a) or (b) of this section of the Food Drug and Cosmetic Act in connection with the development or submission of this application.

It is also hereby certified that Dey Laboratories will not use in any capacity the services of any person debarred under subsection (a) or (b) of this section of the Food Drug and Cosmetic Act in connection with this application.

Further, it is hereby certified that neither Dey Laboratories nor affiliated persons responsible for the development or submission of this application have been convicted within the past five (5) years of offenses described in subsection (a) or (b) of this section of the Food Drug and Cosmetic Act.

Katherine A. Gold
Director, Regulatory Affairs
Dey Laboratories

6/24/96

Date

**APPEARS THIS WAY
ON ORIGINAL**



DEY LABORATORIES
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-0791

July 3, 1996

Request for Waiver of *In Vivo* Evidence of Bioavailability

In accordance with Title 21 of the Code of Federal Regulations, Part 320.22, herein is a request to waive the requirement to demonstrate *in vivo* evidence of bioavailability for Curosurf®.

Curosurf® is a suspension of phospholipids that is administered intratracheally to premature infants to treat respiratory distress syndrome. This request for a waiver of *in vivo* biopharmaceutic studies is based on the medical fragility of premature infants, thus, it is considered not medically feasible to obtain the necessary blood specimens that would be needed to determine bioavailability from a premature neonate. In accordance with 21 CFR 320.22(e), a waiver of the requirement to demonstrate *in vivo* evidence of bioavailability is compatible with the protection of public health.

APPEARS THIS WAY
ON ORIGINAL

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N98
33

April 29, 1998

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

USAN (KK-11)	PORACTANT ALFA
PRONUNCIATION	pore akt' ant
THERAPEUTIC CLAIMS	treatment of respiratory distress syndrome (RDS)
CHEMICAL NAME	
	poractant alfa
DESCRIPTION	
	A purified extract of porcine lungs consisting of a mixture of variable proportions of different phospholipids and hydrophobic proteins. The major constituent is phosphatidylcholine and its disaturated component (dipalmitoylphosphatidylcholine [DPPC]).
TRADEMARK	Curosurf
MANUFACTURER	Chiesi Farmaceutici, S.p.A. (Italy)
<u>CAS</u> REGISTRY NUMBER	129069-19-8
WHO NUMBER	requested

ISI 05/29/98

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 1, 1999

NDA NUMBER: 20-744

NAME OF DRUG: Curosurf (poractant alpha)

NDA HOLDER: Dey, L.P., 2451 Napa Valley Corporate Drive, Napa, CA 94558

I. INTRODUCTION

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570) initially submitted to the Labeling and Nomenclature Committee (LNC) on September 29, 1999 with a request for completion by November 1, 1999.

A previous consult had been requested and completed by the LNC on August 22, 1996. The conclusion of the LNC at that time was as follows:

"The LNC found no look alike/sound alike conflicts with the proprietary name. The Committee was concerned with the use of 'CURO' in the trademark as being misleading, however the name appears to be already in use on the market without any errors attributed to it. The LNC has no reason to find the proposed proprietary name unacceptable."

Curosurf (poractant alpha) is an intratracheal, manufacturer-prepared suspension of pulmonary surfactant extracted from natural porcine lung surfactant¹. Prior to use, Curosurf should be stored in a refrigerator. Curosurf is indicated for the treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants. Administration of exogenous pulmonary surfactant compensates for the deficiency of pulmonary surfactant and restores surface activity to the lungs of premature infants. The initial dose is 2.5mL/kg birth weight. Up to two subsequent doses of 1.25mL/kg birth weight may be administered at 12-hour intervals if needed. Curosurf is supplied in sterile, ready-to-use vials containing 1.5mL or 3mL of suspension. A standard 3 or 5 mL syringe with a needle of at least 20-gauge size is used to withdraw the product from the vial. A pre-cut 8cm 5 French catheter should be attached to the syringe and filled with the suspension. Prior to administering poractant

intratracheally, any extra quantity withdrawn from the vial should be discarded through the catheter so that only the total dose to be given remains in the syringe.

Currently, three other pulmonary surfactant products are marketed in the U.S.ⁱⁱ. Exosurf Neonatal (colfosceril palmitate, Glaxo Wellcome, Approval Date 8/2/1990) is a sterile, lyophilized powder to be reconstituted with Sterile Water for Injection (mfr. supplied) and administered by intratracheal instillation using one of five adapters also provided by the manufacturer. The two other U.S. products (Survanta [beractant, Ross Products, Approval Date 7/1/1991]; Infasurf [calfactant, Forest Pharmaceuticals, Approval Date 7/1/1998]) are manufacturer-prepared liquid suspensions, to be stored under refrigeration. Both products are administered by withdrawing the suspension from the single-use vials with a standard syringe and then instilling the dose intratracheally through a 5 French catheter.

The usual dosage of Exosurf Neonatal suspension is initially 5mL/kg birth weight for prophylaxis and rescue treatment of respiratory distress syndrome (RDS). This dose is repeated 12 hours later for both indications and at 24 hours for prophylaxis. The usual dose of Survanta suspension is 100mg of phospholipids/kg birth weight (4mL/kg). Four doses of Survanta can be administered in the first 48 hours of life and no more frequently than every 6 hours. The usual dosage of Infasurf suspension is 3mL/kg birth weight. Doses have been administered every 12 hours for a total of up to 3 doses.

Curosurf (poractant) appears to be marketed in at least 12 European countries according to standard drug reference textsⁱⁱⁱ.

II. SAFETY AND RISK ASSESSMENT

- A. The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{iii,iv,v} as well as several FDA databases (the Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book) for existing drug names which sound alike or look alike to Curosurf to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A focus group discussion was conducted to review all findings from the searches. *This search and subsequent focus group did not reveal any existing drug names that could cause confusion with Curosurf and thus pose a significant safety risk. A discussion of the use of "CURO" in the trademark was also conducted and no serious safety concerns were raised concerning this phrase.*

- B. A search of the Adverse Event Reporting System (AERS) database was conducted to find any previously reported medication errors for the products on the U.S. market. This search was conducted due to a concern that Curosurf could be injected via other routes of administration. The AERS database was searched for reports using the Meddra term DRUG MALADMINISTRATION where Exosurf[®], Survanta, Curosurf, and Infasurf as well as their corresponding active ingredient substance names were listed as suspect drugs. One report was located using this search. *A 36-week and 5 day-old male infant received 3 mL of Exosurf suspension (colfosceril palmitate) intravenously when a syringe pump was accidentally connected to the umbilical venous catheter. He subsequently experienced seizures that the authors speculated were due to surfactant emboli which*

ultimately led to cerebral arterial ischemia. Neurological and EEG exams at 6 months and 1 year were normal. This case was a recently published literature case^{vi}.

- C. MEDLINE was searched for the 4 drug products with one or more of the following terms: IV, intraven%, art%, veno%, and error. *No other literature reports were located using these search criteria.*

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In reviewing the draft product package insert, container labels, and carton labeling for Curosurf, OPDRA has attempted to focus on safety issues relating to potential medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and the medical officer.

We reviewed the draft product labeling for Curosurf and identified several labeling, packaging, and safety concerns.

A. CARTON LABELING (1.5 mL and 3 mL vials)

1. Delete mg notations of strength on all drug product container labels and carton labeling, with the exception of composition statements. The introduction of mg content (e.g., 120 mg and 240 mg) following the mL notations to these labels increases the likelihood of confusion in dosing since dosing in the draft package insert is specified in milliliters per kilogram, not milligrams per kilogram. Providing a mg content on the vial is therefore inconsistent with the package insert. Note also that the other U.S.-marketed products in this therapeutic category are dosed and labeled in milliliters per kilogram (mL/kg). It would be advisable to maintain this standard across all products.

2. Delete all terminal zeros as they appear on the 3 mL Curosurf drug product container and carton labeling. Specifically, "3.0 mL" should appear as "3 mL" on the labels. Including terminal zeros increases the likelihood of 10-fold dosing errors occurring under usual clinical practice settings^{vii}.

3. The section entitled "COMPOSITION" should be revised to be consistent with the information as provided in the draft package insert. The package insert states "Each milliliter of surfactant mixture contains 80mg of total phospholipids (including 54mg of phosphatidylcholine of which 30.5mg is dipalmitoyl phosphatidylcholine) and 0.8mg of protein including 0.3mg of SP-B." (Emphasis added). The latter ingredient, 0.8mg protein, does not appear on the product container labels or carton labeling as an Active or Inactive ingredient should be included under the appropriate subheading for consistency.

4. Delete one of the two corporate logos (Chiesi or Dey) from the product labels. Although it is required by regulation to include a statement that specifies a manufacturer and/or distributor if the same corporation does not perform both functions, the presence of both logos provides an unnecessary distraction in reading the product labels.

5. Delete the section entitled "CONTENTS:" and its associated information located on the carton panel to the right of the main panel as this information is already provided on the main panel.

6. The heading "INDICATIONS AND DOSAGE" should be revised to "USUAL DOSAGE".

7. Add the statement "DO NOT SHAKE" to the product carton labeling.

B. CONTAINER (1 mL and 3 mL vials)

1. One potential safety concern was discussed previously under SAFETY AND RISK ASSESSMENT. A standard syringe must be used to withdraw the product from the vial containing the product. The vial for Curosurf resembles a vial for intravenous preparations. *After the product has been withdrawn from the vial into a standard, unlabeled syringe, the potential exists for Curosurf to be erroneously administered intravenously or intraarterially.* One documented case of this medication error has been reported to AERS and published in the medical literature^{vi}.

The draft package insert for Curosurf contains the following precaution as the first statement under "DOSAGE AND ADMINISTRATION":

"FOR INTRATRACHEAL ADMINISTRATION ONLY"

We suggest that this statement also be prominently printed on both drug product container label and carton, in addition to "NOT FOR INJECTION".

2. See also comments under CARTON LABELING.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS

- A. From a safety perspective, OPDRA believes that the use of the proposed proprietary name "Curosurf" poses no significant safety risk and, therefore, has no objections to the use of this proprietary name.
- B. OPDRA recommends the above labeling revisions to encourage the safest possible use of this product. We are willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

APPEARS THIS WAY ON ORIGINAL

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur: **APPEARS THIS WAY
ON ORIGINAL**

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc:
NDA 20-744
HFD-570/Division Files/Keary Dunn, Project Manager
HFD-430; Claudia Karwoski, Safety Evaluator, DDREII, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

ⁱ Proposed manufacturer package insert.

ⁱⁱ Product package inserts, PDR.

ⁱⁱⁱ MICROMEDEX Healthcare Intranet Series, 1999, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 1999).

^{iv} American Drug Index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

^v Facts and Comparisons, Updated October 1999, Facts and Comparisons, St. Louis, MO.

^{vi} Frey B, Keller E, Losa M. Seizures after inadvertent umbilical venous infusion of synthetic surfactant (Exosurf): cause or coincidence? *Eur J Pediatr* 1999; 158(7), 610.

^{vii} National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) Council Recommendation. "Recommendations to correct error-prone aspects of prescription writing." Adopted September 4, 1996.

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR TRADEMARK REVIEW

ISI

Q 1/25^m
9-30-99

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Pulmonary and Allergy Drug Products		HFD-570
Attention: Keary Dunn		Phone: (301) 827-1050
Date: September 29, 1999		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Curosurf		NDA/ANDA# NDA 20-744
Established name, including dosage form: poractant alpha		
Other trademarks by the same firm for companion products: N/A		
Indications for Use (may be a summary if proposed statement is lengthy): Infant Respiratory Distress Syndrome (IRDS)		
Initial Comments from the submitter (concerns, observations, etc.): The Division is anticipating approval of this NDA. Original LNC consult done in 1996. Please advise by November 1, 1999.		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-744; HFD-570/division file; HFD-570/Dunn

**APPEARS THIS WAY
ON ORIGINAL**


Consult #644

CUROSURF

poractant suspension

The LNC found no look alike/sound alike conflicts with the proprietary name. The Committee was concerned with the use of "CURO" in the trademark as being misleading, however the name appears to be already in use on the market without any errors attributed to it.

The LNC has no reason to find the proposed proprietary name unacceptable.

 **IS/** 8/22/96, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR CONSULTATION

151
7/10/96
644

TO (Division/Office) Labeling and Nomenclature Committee
Attention: Dan Boring (HFD-530)

FROM:
Division of Pulmonary Drug Products (HFD-570)

DATE
July 9, 1996

IND NO.

NDA NO.
20-744

TYPE OF DOCUMENT
Trademark Review

DATE OF DOCUMENT
7/3/96

NAME OF DRUG: Proposal for
Curosurf (poractant)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
1S

DESIRED COMPLETION DATE
9/3/96

NAME OF FIRM: Dey Labs

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW) |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Is this name acceptable? *see comments on next page.*

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 20-744/Div File HFD-570/Nashed/Schumaker/Kuzmik

SIGNATURE OF REQUESTER
151 7/9/96

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

ATTENTION: Dan Boring, Chief (HFD-570), 5201 Corporate Blvd, Room

644

From: Division of Pulmonary Drug Products		HFD- 570
Attention: Mr. Dan Boring		Phone: 827-2333
Date: July 9, 1996		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Curosurf		NDA# 20-744
Established name, including dosage form: Curosurf (poractant) / <i>Suspension 80mg/mL</i>		
Other trademarks by the same firm for companion products: NA		
Indications for Use (may be a summary if proposed statement is lengthy): Treatment of respiratory distress syndrome in premature infants.		
Initial Comments from the submitter (concerns, observations, etc.): A similar bovine-derived surfactant product, trade name Survanta, has an established name of beractant.		
APPEARS THIS WAY ON ORIGINAL		

BEST POSSIBLE COPY

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ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-744

SEP 3 1998

Dey Laboratories
271 Napa Valley Corporate Drive
Napa, California 94558

Attention: Peggy J. Berry
Regulatory Affairs Manager

Dear Ms. Berry:

Please refer to your new drug application (NDA) dated July 3, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Curosurf (poractant) Intratracheal Suspension.

We acknowledge receipt of your submissions dated March 3 and 19, April 7 and 21, May 15, and July 13 and 28, 1998. Your submission of March 3, 1998 constituted a full response to our July 3, 1997, action letter. The user fee goal date for this application is September 4, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues.

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

11. The following preliminary comments pertain to the labeling. Additional comments will be provided when the above issues have been addressed.
 - a. The product name should be Curosurf (poractant) Intratracheal Suspension.
 - b. The CLINICAL PHARMACOLOGY section should only include data from the two studies that support the effectiveness and safety of Curosurf (i.e., EURO I and EURO IV) for the treatment of RDS.
 - c. The INDICATIONS AND USAGE section should state only that Curosurf is indicated for the treatment of Respiratory Distress Syndrome.
 - d. The ADVERSE REACTIONS section should include a table with complications of prematurity with data from EURO I only.
 - e. The ADVERSE REACTIONS section should also include a statement about the adverse effects generally seen with the administration of Curosurf, e.g., bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation.

- f. The data submitted to the NDA support an initial dose of 200 mg/kg of body weight administered for rescue treatment of Respiratory Distress Syndrome, followed by a maximum of two additional 100 mg/kg doses. This information should be included in the DOSAGE AND ADMINISTRATION, Dosage subsection.
- g. The DOSAGE AND ADMINISTRATION, Directions for Use subsection should only contain information on the administration of Curosurf into each main bronchus via a feeding tube. The data submitted in the NDA do not support the administration of Curosurf as a bolus into the lower trachea as proposed in the package insert.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

You are advised to contact the Division of Pulmonary Drug Products regarding the extent and format of your safety update prior to submitting your complete response to this letter.

In addition, although not required prior to approval, we have the following comments and request for information that should be addressed.

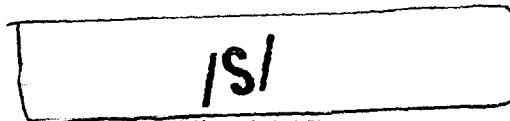
Based on our review of the data submitted in the NDA, we have concluded that studies EURO I and EURO IV support the effectiveness and safety of Curosurf for the treatment of Respiratory Distress Syndrome (RDS) in premature infants.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Dr. Denise Toyer, Project Manager, at (301) 827-5584.

Sincerely,



James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

7 pages

NDA 20-744

Page 9

You are advised to contact the Division of Pulmonary Drug Products regarding the extent and format of your safety update prior to submitting your complete response to this letter.

Since poractant is not an established name as described under 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, you should apply to the United States Adopted Names (USAN) Council for adoption of a name that will comply with that section of the Act. They can be contacted at the following address:

NDA 20-744
Page 10

U.S. Adopted Names Council
American Medical Association
P.O. Box 10970
Chicago, IL 60610

We reserve comment regarding your label and labeling until the application is otherwise approvable.


As communicated to you in our letter dated May 28, 1996, due to the orphan exclusivity granted to Ross Laboratories' product Survanta, this application may not be finally approved until July 1, 1998, unless you can show to our satisfaction that Curosurf and Survanta should not be considered to be "the same drug" under the Orphan Drug Regulations.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division of Pulmonary Drug Products to discuss what further steps need to be taken before the application may be approved.

Should you have any questions, please contact Ms. Betty Kuzmik, Project Manager, at 301-827-1051.

Sincerely yours,



7/3/97

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FEB 29 1996

STANDARD METHODS

FOR THE
EXAMINATION OF
WATER AND
WASTEWATER

18TH EDITION 1992

Prepared and published jointly by:

AMERICAN PUBLIC HEALTH ASSOCIATION
AMERICAN WATER WORKS ASSOCIATION
WATER ENVIRONMENT FEDERATION

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Managing Editor

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Publication Office

American Public Health Association
1015 Fifteenth Street, NW
Washington, DC 20005

17 FEB 29 1996

2010 INTRODUCTION

This part deals primarily with measurement of the physical properties of a sample, as distinguished from the concentrations of chemical or biological components. Many of the determinations included here, such as color, electrical conductivity, and turbidity, fit this category unequivocally. However, physical properties cannot be divorced entirely from chemical composition, and some of the techniques of this part measure aggregate properties resulting from the presence of a number of constituents. Others, for example, calcium carbonate saturation, are related to, or depend on, chemical tests. Also included here are

tests for appearance, odor, and taste, which have been classified traditionally among physical properties, although the point could be argued. Finally, Section 2710, Tests on Sludges, includes certain biochemical tests. However, for convenience they are grouped with the other tests used for sludge.

With these minor exceptions, the contents of this part have been kept reasonably faithful to its name. Most of the methods included are either inherently or at least traditionally physical, as distinguished from the explicitly chemical, radiological, biological, or bacteriological methods of other parts.

2020 QUALITY CONTROL

Part 2000 contains a variety of analytical methods, many of which are not amenable to standard quality-control techniques. General information on quality control is provided in Part 1000 and specific quality-control techniques are outlined in the individual methods. The following general guidelines may be applied to many of the methods in this part:

Evaluate analyst performance for each method. Determine competence by analyses of samples containing known concentrations.

Calibrate instruments and ensure that instrument measurements do not drift.

Assess the precision of analytical procedures by analyzing at least 10% of samples in duplicate. Analyze a minimum of one duplicate with each set of samples.

Determine bias of an analytical procedure in each sample batch by analysis of blanks, known additions with a frequency of at least 5% of samples, and, if possible, an externally provided standard.

2110 APPEARANCE*

To record the general physical appearance of a sample, use any terms that briefly describe its visible characteristics. These

terms may state the presence of color, turbidity, suspended solids, crustacea, larvae, worms, sediment, floating material, and similar particulate matter detectable by the unaided eye. Use numerical values when they are available, as for color, turbidity, and suspended solids.

*Approved by Standard Methods Committee, 1988.

2120 COLOR*

2120 A. Introduction

Color in water may result from the presence of natural metallic ions (iron and manganese), humus and peat materials, plankton, weeds, and industrial wastes. Color is removed to make a water suitable for general and industrial applications. Colored industrial wastewaters may require color removal before discharge into watercourses.

1. Definitions

The term "color" is used here to mean true color, that is, the color of water from which turbidity has been removed. The term "apparent color" includes not only color due to substances in solution, but also that due to suspended matter. Apparent color is determined on the original sample without filtration or centrifugation. In some highly colored industrial wastewaters color is contributed principally by colloidal or suspended material. In

* Approved by Standard Methods Committee, 1988.

such cases both true color and apparent color should be determined.

2. Pretreatment for Turbidity Removal

To determine color by currently accepted methods, turbidity must be removed before analysis. The optimal method for removing turbidity without removing color has not been found yet. Filtration yields results that are reproducible from day to day and among laboratories. However, some filtration procedures also may remove some true color. Centrifugation avoids interaction of color with filter materials, but results vary with the sample nature and size and speed of the centrifuge. When sample dilution is necessary, whether it precedes or follows turbidity removal, it can alter the measured color if large color-bodies are present.

Acceptable pretreatment procedures are included with each method. State the pretreatment method when reporting results.

3. Selection of Method

The visual comparison method is applicable to nearly all samples of potable water. Pollution by certain industrial wastes may produce unusual colors that cannot be matched. In this case use an instrumental method. A modification of the tristimulus and the spectrophotometric methods allows calculation of a single color value representing uniform chromaticity differences even when the sample exhibits color significantly different from that of platinum cobalt standards. For comparison of color values among laboratories, calibrate the visual method by the instrumental procedures.

4. Bibliography

- OPTICAL SOCIETY OF AMERICA. 1943. Committee Report. The concept of color. *J. Opt. Soc. Amer.* 33:544.
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2120 B. Visual Comparison Method

1. General Discussion

a. Principle: Color is determined by visual comparison of the sample with known concentrations of colored solutions. Comparison also may be made with special, properly calibrated glass color disks. The platinum-cobalt method of measuring color is the standard method, the unit of color being that produced by 1 mg platinum/L in the form of the chloroplatinate ion. The ratio of cobalt to platinum may be varied to match the hue in special cases; the proportion given below is usually satisfactory to match the color of natural waters.

b. Application: The platinum-cobalt method is useful for measuring color of potable water and of water in which color is due to naturally occurring materials. It is not applicable to most highly colored industrial wastewaters.

c. Interference: Even a slight turbidity causes the apparent color to be noticeably higher than the true color; therefore remove turbidity before approximating true color by differential reading with different color filters¹ or by differential scattering measurements.² Neither technique, however, has reached the status of a standard method. Remove turbidity by centrifugation or by the filtration procedure described under Method C. Centrifuge for 1 h unless it has been demonstrated that centrifugation under other conditions accomplishes satisfactory turbidity removal.

The color value of water is extremely pH-dependent and invariably increases as the pH of the water is raised. When reporting a color value, specify the pH at which color is determined. For research purposes or when color values are to be compared among laboratories, determine the color response of a given water over a wide range of pH values.³

d. Field method: Because the platinum-cobalt standard method is not convenient for field use, compare water color with that of glass disks held at the end of metallic tubes containing glass comparator tubes filled with sample and colorless distilled water. Match sample color with the color of the tube of clear water plus the calibrated colored glass when viewed by looking toward a

white surface. Calibrate each disk to correspond with the colors on the platinum-cobalt scale. The glass disks give results in substantial agreement with those obtained by the platinum-cobalt method and their use is recognized as a standard field procedure.

e. Nonstandard laboratory methods: Using glass disks or liquids other than water as standards for laboratory work is permissible only if these have been individually calibrated against platinum-cobalt standards. Waters of highly unusual color, such as those that may occur by mixture with certain industrial wastes, may have hues so far removed from those of the platinum-cobalt standards that comparison by the standard method is difficult or impossible. For such waters, use the methods in Sections 2120C and D. However, results so obtained are not directly comparable to those obtained with platinum-cobalt standards.

f. Sampling: Collect representative samples in clean glassware. Make the color determination within a reasonable period because biological or physical changes occurring in storage may affect color. With naturally colored waters these changes invariably lead to poor results.

2. Apparatus

- a. Nessler tubes*, matched, 50-mL, tall form.
b. pH meter, for determining sample pH (see Section 4500-H⁺).

3. Preparation of Standards

a. If a reliable supply of potassium chloroplatinate cannot be purchased, use chloroplatinic acid prepared from metallic platinum. Do not use commercial chloroplatinic acid because it is very hygroscopic and may vary in platinum content. Potassium chloroplatinate is not hygroscopic.

b. Dissolve 1.246 g potassium chloroplatinate, K_2PtCl_6 (equivalent to 500 mg metallic Pt) and 1.00 g crystallized cobaltous chloride, $CoCl_2 \cdot 6H_2O$ (equivalent to about 250 mg metallic Co)

COLOR (2120)/Spectrophotometric Method

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in distilled water with 100 mL conc HCl and dilute to 1000 mL with distilled water. This stock standard has a color of 500 units.

c. If K_2PtCl_6 is not available, dissolve 500 mg pure metallic Pt in aqua regia with the aid of heat; remove HNO_3 by repeated evaporation with fresh portions of conc HCl. Dissolve this product, together with 1.00 g crystallized $CoCl_2 \cdot 6H_2O$, as directed above.

d. Prepare standards having colors of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, and 70 by diluting 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, and 7.0 mL stock color standard with distilled water to 50 mL in nessler tubes. Protect these standards against evaporation and contamination when not in use.

4. Procedure

a. *Estimation of intact sample:* Observe sample color by filling a matched nessler tube to the 50-mL mark with sample and comparing it with standards. Look vertically downward through tubes toward a white or specular surface placed at such an angle that light is reflected upward through the columns of liquid. If turbidity is present and has not been removed, report as "apparent color." If the color exceeds 70 units, dilute sample with distilled water in known proportions until the color is within the range of the standards.

b. Measure pH of each sample.

5. Calculation

a. Calculate color units by the following equation:

$$\text{Color units} = \frac{A \times 50}{B}$$

where:

- A = estimated color of a diluted sample and
B = mL sample taken for dilution.

b. Report color results in whole numbers and record as follows:

Color Units	Record to Nearest
1-50	1
51-100	5
101-250	10
251-500	20

c. Report sample pH.

6. References

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3. BLACK, A.P. & R.F. CHRISTMAN. 1963. Characteristics of color surface waters. *J. Amer. Water Works Assoc.* 55:753.

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KUZMIR

NDA 20-744

NOV 19 1996

Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Attention: Randall Miller
Director, Regulatory Affairs

Dear Mr. Miller:

Please refer to your pending new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Curosurf Intratracheal Suspension.

We have completed our review of the environmental assessment and microbiology sections of your submission and have the following comments and requests for information.

1. Dey Laboratories of Napa Valley California is the applicant for NDA 20-744, yet the Environmental Assessment is signed by the _____ of the Chiesi Farmaceutici facility. Submit certification (format item 13) from the responsible official of Dey Laboratories, which can be appended to your Environmental Assessment.
2. The following comments pertain to the overall manufacturing operation.

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2 pages

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We would appreciate your prompt written response so we can continue our evaluation of your NDA.

Should you have any questions, please contact Ms. Betty Kuzmik, Project Manager, at 301-827-1051.

Sincerely yours,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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