CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021746Orig1s000

CHEMISTRY REVIEW(S)

NDA 21-746

Surfaxin (lucinactant) Intratracheal Suspension

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Discovery Laboratories, Inc.
2600 Kelly Road, Suite 100,
Warrington, PA 18976-3622

Indication: **P**revention of respiratory distress syndrome (RDS) in premature infants.

Presentation: The drug product suspension is sterile-filled to 8.5 mL in 10 mL sterile glass vials and contains 0.862 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG and 4.05 mg/mL of PA, total 8.5 mL per vial. This corresponds to a concentration of 0.862 mg of peptide and 30 mg of total phospholipids per 1 mL of drug product suspension.

EER Status: Acceptable, March 2, 2012

Consults:	EA –	Categorical exclusion provided
	Statistics –	N/A
	Methods Validation –	Not recommended
	Biopharm–	N/A
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Original Submission:	14-April-2004
Re-submissions:	2-Sept-2011 (see amendments listed in CMC reviews)

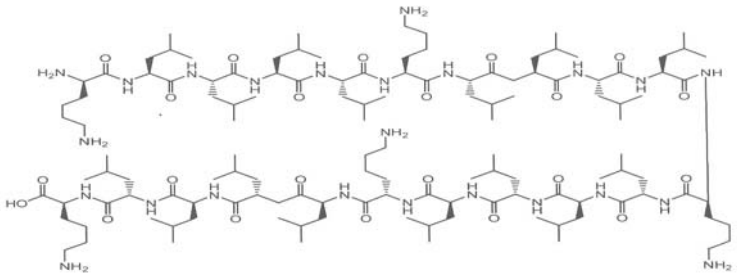
Post-Approval CMC Agreements: Yes.

Firm commits to submission of a prior approval supplement to implement a change: Transfer of "Data Analysis and Oversight" of the fetal rabbit bioassay method (DP32) from the Discovery Warrington, PA site to the (b) (4)

Background:
This NDA was submitted in April 2004; the drug product has had an orphan drug designation since 10/18/95;
It is important to report here that, since 2004 and after five review cycles; the NDA is finally ready for approval from a CMC standpoint.

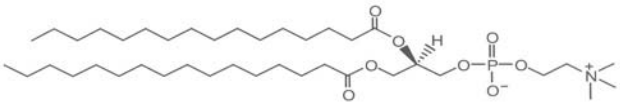
Drug Substance:
There are four active pharmaceutical ingredients (APIs) in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

- **Sinapultide**
  L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-Llysyl-
  L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine. Chemical Structure



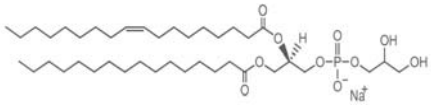
Molecular formula: $C_{126}H_{239}N_{26}O_{22;}$ Molecular weight: 2470

- **DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)** Chemical Structure



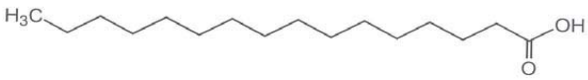
Molecular formula: $C_{40}H_{80}NO_8P$; Molecular weight: 734.05

- **POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)** Chemical Structure



Molecular formula: $C_{40}H_{76}NPO_{10}Na$; Molecular weight: 771.00

- **PA (palmitic acid; hexadecanoic acid)** Chemical Structure



Molecular formula: $C_{16}H_{32}O_{2;}$ Molecular weight: 256.42

CMC information related to each of the above APIs is supported by the corresponding Drug Master Files. All Drug Master Files (DMFs) associated with the drug substances were reviewed and found acceptable.

Conclusion: Drug substance is acceptable.

Drug Product:

(b) (4) The drug product suspension (8.5 mL nominal fill) is aseptically packaged into a sterile 10 mL glass vial (USP Type I (b) (4) glass) sealed with (b) (4) gray rubber stopper and red flip-off aluminum seal.

Specifications for SURFAXIN (lucinactant) include: appearance; identification of four active ingredients; assay of four active ingredients; impurities (b) (4) (b) (4) pH; surface tension; *in vivo* activity; viscosity; sterility; bacterial endotoxins; particulates; and particle size.

The drug product consists of an aqueous suspension (b) (4) of a synthetic, 21-amino acid peptide (sinapultide), dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG) and palmitic acid (PA). The amino acid sequence of the sinapultide (KL_4) was designed to simulate the natural structure of the lung surfactant protein B (SP-B). However, it is noted that the (b) (4) to mimic the behavior of the *in vivo* system responsible for lowering surface tension in the lungs.

The drug product suspension is sterile-filled to 10 mL sterile glass vials and contains 0.862 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG and 4.05 mg/mL of PA, total 8.5 mL per vial. This corresponds to a concentration of 0.862 mg of peptide and 30 mg of total phospholipids per 1 mL of drug product suspension.

Surfaxin (lucinactant) Intratracheal Suspension is intended for the prevention of respiratory distress syndrome (RDS) in premature infants. It is a milky white suspension intended for an intratracheal instillation to the lungs of premature neonates in a hospital setting. The proposed dose for Surfaxin is 5.8 mL/kg body weight for up to four doses in the first 48 hours of life. The exact administered dose is determined by the attending physician based on the weight of the neonate.

The nominal fill is 8.5 mL of suspension per 10 mL sterile vial to be stored at 5°C ± 3 °C (refrigerator). Before the use, the suspension needs to be warmed up by placing the vial in a dry block heater set at 44°C (111°F) for 15 minutes. The warmed drug product has to be used within 2 hours of warming. Vials are for single use only and any unused portion of the drug has to be discarded.

The submitted stability data support the requested expiry period of 12 months for the currently manufactured drug product, when stored at 2-8°C.

Conclusion: Drug product is satisfactory.

Overall Conclusion:
From a CMC perspective, the application is recommended for approval.

Eric Duffy, Ph.D.
Director
DPA III/ONDQA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P DUFFY
03/06/2012

NDA 21-746

Surfaxin (lucinactant) Intratracheal Suspension

Discovery Laboratories, Inc.

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division III, Branch 8

for

Division of Pulmonary, Allergy and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA 21-746

2. REVIEW # 5 Addendum

3. REVIEW DATE: 2-March-2012

4. REVIEWER: Eugenia M. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Submissions Reviewed Previously (Review Cycles 1-4)	Document Date	CDER Date	Assigned Date
Original **NDA**	13-Apr-2004	15-Apr-2004	26-Apr-2004
Amendment	29-Jun-2004	30-Jun-2004	12-Jul-2004
Amendment	13-Sep-2004	14-Sep-2004	16-Sep-2004
Amendment	19-Oct-2004	20-Oct-2004	25-Oct-2004
Amendment	15-Nov-2004	16-Nov-2004	24-Nov-2004
Amendment	23-Nov-2004	26-Nov-2004	13-Dec-2004
Amendment	04-Jan-2005	05-Jan-2005	10-Jan-2005
Amendment	06-Jan-2005	10-Jan-2005	18-Jan-2005
Amendment **AZ**	05-Oct-2005	11-Oct-2005	19-Oct-2005
Amendment BC	20-Jan-2006	24-Jan-2006	25-Jan-2006
Amendment **AZ**	31-Oct-2007	01-Nov-2007	19-Nov-2007
Amendment BC	05-Dec-2007	06-Dec-2007	17-Dec-2007
Amendment BC	07-Dec-2007	10-Dec-2007	23-Dec-2007
Amendment BC	20-Dec-2007	20-Dec-2007	10-Jan-2008
Amendment BC	21-Dec-2007	26-Dec-2007	10-Jan-2008
Amendment BC	18-Jan-2008	23-Jan-2008	11-Feb-2008
Amendment BC	29-Feb-2008	29-Feb-2008	13-Mar-2008
Amendment **AZ**	17-Oct-2008	20-Oct-2008	28-Oct -2008
Amendment BC	12-Feb-2009	13-Feb-2009	18-Feb-2009

6. SUBMISSIONS BEING REVIEWED:

Submissions Reviewed	Document Date	CDER Date	Received Date

Reference ID: 3096671

Amendment **AZ**	02-Sep-2011	06-Sep-2011	15-Sep-2011
Amendment BC	10-Oct-2011	11-Oct-2011	16-Oct-2011
Amendment BC	14-Nov-2011	15-Nov-2011	21-Nov-2011
Amendment BZ	16-Jan-2012	17-Jan-2012	25-Jan-2012
Amendment BZ	19-Jan-2012	20-Jan-2012	02-Feb-2012
Amendment BZ	23-Jan-2012	24-Jan-2012	30-Jan-2012
Amendment BZ	01-Mar-2012	02-Mar-2012	02-Mar-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Discovery Laboratories, Inc.

Address: 2600 Kelly Road, Suite 100, Warrington, PA 18976-3622

Representative: Russell G. Clayton Sr., Senior Vice President., Research and Development Tel.: 215-488-9470

1. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Surfaxin

b) Non-Proprietary Name (USAN): Lucinactant Intratracheal Suspension

c) Code Name/# (ONDC only): KL_4

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

2. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Lung surfactant for premature infants

11. DOSAGE FORM: Intratracheal Suspension, 5.8 mL/kg body weight

12. STRENGTH/POTENCY: 0.862 mg/mL sinapultide, 22.5 mg/mL DPPC, 7.5 mg/mL POPG and 4.05 mg/mL PA.

13. ROUTE OF ADMINISTRATION: Intratracheal

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14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

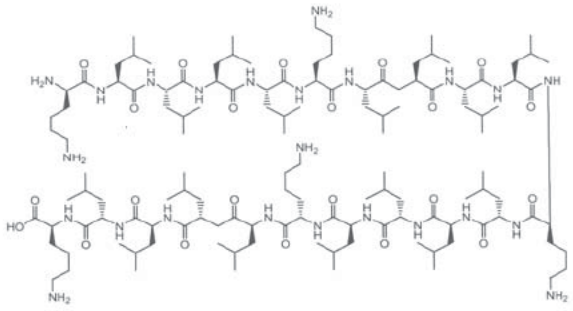
___X___Not a SPOTS product

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

There are four active pharmaceutical ingredients (APIs) in this drug product: 21-aa synthetic peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA). Together they form the active structure of lucinactant.

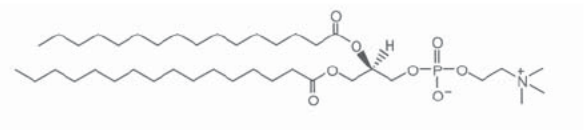
- **Sinapultide** - New Molecular Entity (NME)

L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine, acetate.



CAS 138531-07-4
Molecular formula: $C_{126}H_{238}N_{26}O_{22}$
Molecular weight: 2469.46

- **DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)**



CAS 63-89-8
Molecular formula: $C_{40}H_{80}NO_8P$
Molecular weight: 734.05

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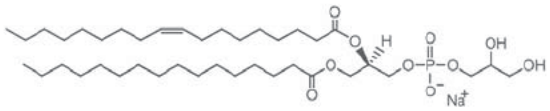
- **POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol) sodium**



CAS 13879-80-6
Molecular formula: $C_{40}H_{76}NPO_{10}Na$
Molecular weight: 771.00

- **PA (palmitic acid; hexadecanoic acid)**

CAS 57-10-3
Molecular formula: $C_{16}H_{32}O_2$
Molecular weight: 256.42

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	ADEQUATE Inadequate Inadequate	Rev #3: 11/3/05 Suong T. Tran Rev #2: 10/7/04 Rev #1: 7/9/04	The updates to the DMFs provided after the last review date do not contain any changes or data that would warrant an inadequate status indication for this DMF. Originally, 23 deficiencies were forwarded to the holder. Second review listed 7 remaining deficiencies. Review #3 yielded an Adequate status.
	II			1	ADEQUATE Inadequate Inadequate	1/26/12 Art Shaw 3/1/06 Eugenia Nashed 1/18/05 Edwin Jao	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet. Originally, the DMF lacked adequate specifications for impurities and sufficient stability data.
	II				ADEQUATE	1/26/12 Art Shaw	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet

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(b) (4)	II	(b) (4)	(b) (4)	1	ADEQUATE IR letter pending	1/26/12 Art Shaw 4/15/08 Art Shaw	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet. Originally, the DMF contained inadequate impurity profile and stability data, but the issues are resolved.
	II			1	ADEQUATE IR letter pending Inadequate	1/26/12 Art Shaw 3/28/08 Art Shaw 1/19/05 Art Shaw	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet. Originally, the DMF contained inadequate impurity profile and stability data, but the issues are resolved.
	II			1	ADEQUATE Adequate Inadequate Inadequate	1/26/12 Art Shaw 3/20/08 Art Shaw 3/2/06 Eugenia Nashed 1/14/05 Edwin Jao	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet. Originally, the DMF contained inadequate impurity profile and stability data, but the issues are resolved.
(b) (4)	II	(b) (4)	(b) (4)	1	DMF WITHDRAWN Inadequate Inadequate	3/7/06 Vinayak Pawar 1/18/05 Vinayak Pawar	The applicant purchased the manufacturing facility and became the new owner (1/06) of the DMF. DMF was withdrawn from the application on Oct 31, 2007. Two previous reviews of the DMF identified number of serious deficiencies. The issues were addressed during subsequent GMP inspections.
(b) (4)	I	(b) (4)	(b) (4)	5	Not reviewed		Type I DMF. Facility is no longer involved in the drug manufacturing or testing.
(b) (4)	III	(b) (4)	(b) (4)	1	ADEQUATE	11/10/10 Joel Hathaway	
	III			1	ADEQUATE	9/18/11	Also, adequate for similar

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		(b) (4)	(b) (4)			Kristen Anderson	formulation Rev 8/26/03 by J. Salemme, HFD-580.
(b) (4)	III				ADEQUATE	9/27/11 Marla Stevens Riley	Microbiology evaluation.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 40,287 (b) (4)	Discovery Laboratories	Surfaxin Intratracheal Suspension	Active	N/A	IND drug product batches were manufactured at the (b) (4) site, which has "WITHHOLD" recommendation due to the multiple GMP violations (several inspections).

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EER (GMP)	GMP compliance for DS and DP manufacturing and testing sites	EER update resubmitted Oct 2011 EER update resubmitted in Nov 2007 EER update resubmitted in Nov 2005 5/11/04	Mar 2, 2012: ACCEPTABLE, **with re-evaluation scheduled for Mar 9, 2012** <u>Prior Review Cycles:</u> Sep 17, 2008: Acceptable May 2008: Withhold Approval Apr 2006: Withhold Approval Feb 2006: Withhold Approval	**Drug Product Manufacturing Site** The drug product manufacturing site in Totowa, NJ, was re-inspected in Jan 2012, to evaluate the manufacturing changes implemented in May 2011, to the sterile fill process. The site received AC recommendation on Feb 7, 2012. Previous GMP inspection in Apr 2008, resulted in Acceptable recommendation in Sep 2008, after adequate correction of deficiencies listed on FDA Form 483. All five prior inspections identified serious GMP deficiencies at this sterile fill manufacturing site (Totowa, NJ). Also, the prior manufacturing site for clinical

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			Oct 2005: Withhold Approval Feb 2005: Withhold Approval	batches at (b) (4) received several FDA Forms 483 and was not able to secure an acceptable recommendation from the ORA.
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GLP/GMP	GLP compliance of the testing in premature rabbits. Method execution and validation for testing the Biological Activity of drug product in fetal rabbits (FRBAT method)	10/2011 (DPARP) and second part of inspection 01/2012 (DPARP)	Mar 2, 2012: ACCEPTABLE for data integrity, however Method DP-032 not conducted in compliance with CFR Part 58. Dec 16, 2011: Form 483 with seven GLP deficiencies was issued to the (b) (4) site. Feb 24, 2011: Form 483 with 6 GLP/GMP deficiencies was issued to the Warrington, PA site.	**FRBAT Testing Sites** Two sites are involved in testing the biological activity of drug product biological activity in premature rabbits (FRBAT). The NDA resubmission dated Sep 6, 2011, listed only one site, (b) (4) DPARP requested a GLP evaluation of the testing performed on premature rabbits, since the method is pivotal for linking the efficacy of the currently manufactured drug product to the drug product used in clinical trials. Also, the same method is used for the release and stability testing of the drug product. The inspection performed at the (b) (4) revealed serious GLP violations and the fact that part of the method is carried out at another facility, Discovery Laboratories at Warrington, PA (Raw data analysis, interpretation, and reporting). An inspection of Warrington facility was requested by DPARP. The final Inspection conclusions recommend improvements in documentation practices – refer to Inspection Report by Dr. Charles Bonapace dated Mar 2, 2012. Also, refer to the pending Phase 4 Commitment by the Applicant regarding future consolidation of the biological activity testing method at the (b) (4).
Pharm/Tox	1) Scientific merit and validation of the FRBAT method for testing biological activity of the drug product in premature rabbits. The method is used for efficacy linking of the currently manufactured drug product to the product used in clinical studies. Also, it is used as a	09/2012 11/2008 10/19/06 11/15/05	ACCEPTABLE 2/28/12 <u>Prior Review Cycles:</u> Inadequate 3/4/09, Luqi Pei Inadequate 3/11/08, Huiqing Hao Inadequate 3/3/06, Huiqing Hao	The scientific merits and the method validation for the proposed FRBAT method are considered adequate to support the use of the method as a regulatory release and stability testing and also, for linking the activity of the currently manufactured drug product to the drug product used in clinical trials. Refer to reviews dated 2/28/12 and 12/12/11, by Drs. Luqi Pei and Timothy Robinson, with input from Dr. Jinglin Zhong, Mathematic Statistician.

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	regulatory release and stability testing method for the drug product. 2) Qualification of impurities in drug substance and drug product.	05/2004 09/2012 05/2004	Inadequate 12/01/04, Huiqing Hao <u>Current Status</u>: ADEQUATE 12/12/11, Luqi Pei Inadequate in the prior five review cycles.	All issues pertaining to the qualification of drug substance and drug product impurities are adequately resolved in this review cycle – refer to PharmTox review dated 12/12/11.
Biopharm	N/A			
Methods Validation				No MV deem necessary at this point.
Division Of Medication Error Prevention and Analysis	Assessment of the proposed proprietary name	7/16/04	<u>Current Status</u>: AC 01/24/12 Carol Holquist <u>Prior Review Cycles:</u> Inadequate Inadequate Denise Toyer 3/1/06 Inadequate Denise Toyer 11/8/04	Acceptable Name acceptable from promotional perspective. NOT RECOMMENDED due to sound-like and look-like similarities with other drug names. The name Surfaxin is NOT RECOMMENDED + labeling comments concerning safety
DDMAC	Adequacy of PI	7/16/04	Acceptable Inadequate Jialynn Wang 10/18/04	Label needs minor revisions
EA	Exclusion requested	N/A	Acceptable	See CMC review #1
Microbiology	Sterile manufacture, fill and testing of the drug product.	10/2011 5/10/04	<u>Current Status</u>: Acceptable <u>Prior Review Cycles:</u> Adequate Inadequate 3/7/06, V. Pawar Inadequate 1/18/05, V. Pawar	Review dated Feb 7, 2012, is in DARRTS.

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The Chemistry Review for NDA 21-746

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC review team recommends an APPROVAL action for this NDA, based on satisfactory CMC data submitted in support of the NDA, adequate recommendation from the Pharmacology and Toxicology team (review of the method testing drug product biological activity in premature rabbits), satisfactory recommendation from the Microbiology review team (sterile fill manufacturing process and microbial safety controls) and ACCEPTABLE recommendation from the ORA dated Mar 2, 2012.

The requested expiry period for the drug product is 12 months and it is supported by the submitted data. The CMC team recommends that the extension of the expiry period be accomplished only *via* a prior-approval (PA) supplemental application with adequate supporting stability data. This restriction is recommended due to the observed instability of the drug product formulation (refer to Section II. C, of the Summary below), recent changes to the manufacturing process and pending changes to the responsibility for QA and data analysis functions for the biological activity testing of the drug product (FRBAT method).

This NDA was submitted in April 2004, and was burdened with serious manufacturing shortcomings and control deficiencies. After five review cycles and numerous meetings with the Applicant providing regulatory guidance and advice, all remaining CMC deficiencies have been resolved. The anticipated changes to the QA and data analysis functions for the FRBAT method are addressed in the proposed commitment below, and evaluated in detail further down in this review (page 19).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Based on the conclusions of the GLP/GMP inspections carried out at the facilities involved in testing biological activity of the drug product and in agreement with the NDA amendment dated Mar 1, 2012, the following Phase 4 Commitment is proposed to the action letter:

You commit to submit, by January 30, 2014, a prior-approval (PA) supplemental application to describe, and provide supporting data as needed, changes in the

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responsibilities for quality assurance and data analysis pertaining to the analytical method DP-32 for testing biological activity of the drug product. While no changes are anticipated to the current analytical method (DP-032 revision 05), the personnel training, installation of additional equipment, implementation of appropriate standard operating procedure (SOP) for data analysis, review, documentation practices, deviation and investigation, corrective and preventive action (CAPA) is anticipated to be completed by Sep 2012, as described in NDA amendment dated March 1, 2012. The PA supplemental application will state that the analytical facility at the (b) (4) (b) (4) *is ready for inspection and it is qualified to assume full responsibility for all functions related to Method DP-032, including data QA and analysis. The transfer of responsibilities from Discovery to* (b) (4) *will occur upon the approval of PA supplemental application by the Agency.*

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This is a complex drug product (lucinactant) where several active ingredients need to interact (b) (4). It consists of an aqueous suspension, in a (b) (4), of a synthetic, 21-amino acid KL_4 peptide (sinapultide), dipalmitoyl-phosphatidylcholine (DPPC), palmitoyloleoylphosphatidylglycerol sodium (POPG, Na) and palmitic acid (PA). The amino acid sequence of sinapultide peptide comprises of four repeating units made of one lysine and four leucines (KL_4). It is a New Molecular Entity (NME) and it is designed (b) (4) to simulate the nature of the structure characteristic for the lung surfactant protein B (SP-B). (b) (4). The combination of these four active ingredients was designed to mimic the behavior of the *in vivo* lung surfactant system responsible for lowering surface tension in the lungs of premature infants. The biological activity of the drug (b) (4) of the combination and it is controlled by the testing of lung function in premature rabbits (FRBAT test).

There are four active ingredients in this drug product: 21-amino acid peptide (sinapultide), two phospholipids (DPPC and POPG, Na), and palmitic acid (PA). Each API is supported and by a corresponding DMF and controlled by the acceptance criteria specifications. The current status is "Adequate" for each DMF – refer to the "Supporting DMFs" table above in this review.

The drug product suspension is manufactured by a (b) (4)

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(b) (4) 10 mL sterile glass vials in a (b) (4) facility. The final concentration is adjusted to 0.862 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG, Na (30 mg/mL of total phospholipids) and 4.05 mg/mL of PA. The pH of the suspension is 7.4. The nominal fill per vial is 8.5 mL, (b) (4) The drug product forms a gel-like white suspension at the room temperature and needs to be warmed up to 40ºC, to achieve a free flowing consistency before the administration. It is administered in a hospital setting *via* intratracheal tube and the recommended dose is 5.8 mL per kg body weight of the infant.

B. Description of How the Drug Product is Intended to be Used

Surfaxin (lucinactant) Intratracheal Suspension is intended for the prevention of Respiratory Distress Syndrome (RDS) in premature infants. It is a milky-white suspension intended for an intratracheal instillation to the lungs of premature neonates in a hospital setting. The recommended dose for Surfaxin is 5.8 mL/kg body weight for up to four doses in the first 48 hours of life. The exact dose for administration is determined by the attending physician based on the weight of the neonate. The recommended dosing chart is included in the package insert.

The nominal fill is 8.5 mL of drug product suspension per 10 mL sterile vial to be stored at 5°C ± 3 °C (refrigerator). Before the use, the suspension needs to be warmed up by placing the vial in a dry block heater set at 44°C (111°F) for 15 minutes. The warmed drug product has to be used within 2 hours of removing from the refrigerator. Vials are for single use only and any unused portion of the drug has to be disposed.

C. Basis for Approvability or Not-Approval Recommendation

This application is recommended for approval from the CMC perspective. Consult reviews assured satisfactory recommendations from the Pharmacology and Toxicology team (evaluation of the FRBAT method for drug product biological activity in premature rabbits, review by Dr. Luqi Pei dated Feb 28, 2012), and Microbiology review team (sterile fill process and microbial safety controls). Also, an acceptable recommendation from the ORA is available as of Mar 2, 2012 (see copy on page 25 of this review).

The status of major review issues emphasized during this review cycle to support the CMC recommendation is summarized below.

- Biological Activity (Potency) of the Drug Product

  The potency of this complex drug product mixture is tested in premature rabbits (FRBAT method) by assessing the lung function (respiratory system compliance,

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C_{RS} = $\Delta V/\Delta P$) after instillation of the drug product and in comparison to the negative and positive (approved lung surfactant) controls. The FRBAT method is used for bridging the activity of the currently manufactured drug product to the drug product used in clinical trials and also as a release and stability testing method. The original NDA application has lacked an adequately validated method and data for drug product biological activity and the method was considered inadequate after four review cycles, despite several feedback letters and multiple meetings with the Applicant. Refer to Pharmacology and Toxicology reviews dated Mar 4, 2009, by Dr. Luqi Pei, and Mar 11, 2008, by Dr. Huiqing Hao.
In this review cycle a team comprised of the Pharmacology and Toxicology reviewer, the Statistics reviewer and this reviewer worked closely with the Applicant for several months by reviewing in depth submissions provided to IND 40,287, associated with this NDA, with subsequent versions of the method and method validation corrected based on our feedback comments, and finally reviewing the complete response to the NDA. Based on the submitted data the Version 2 of the method's validation seems acceptable to our team. However, after the GLP inspection at the rabbit testing site (b) (4) the investigator noted that part of the method (raw data processing, data evaluation and reporting, and method validation) is performed at a different site (Discovery site at Warrington, PA) and the data integrity can not be assured without a second inspection tracking the data and assuring data integrity. In addition, a multiple GLP deficiencies were reported on FDA form 483 for the (b) (4) site. The method was changed and version 5 of the method seems to be currently in use. The DPARP requested a follow up directed GLP inspection to complete the data tracking since the FRBAT method is pivotal for bridging the efficacy of the drug product and establishing adequate drug product controls. The inspection at the Warrington, PA site resulted in FDA Form 483 with 6 deficiencies. The Applicant addressed satisfactory all deficiencies issued by the join GLP/GMP Investigation team. Also, a commitment was provided (NDA amendment dated Mar 1, 2012) to transfer the QA and data analysis to the (b) (4) testing site – Refer to detail evaluation on page 19 of this review.

- Limited Drug Product Stability

From the CMC perspective the most serious concern pertains to the limited stability of the drug product (b) (4) (based on the submitted Circular Dichroism data) and decreases the biological activity of the drug product. A substantial decline in the biological activity (*ca* 25% decrease over 12 months) and an increase in the surface tension is noted during the storage in refrigerator (Label storage conditions). The loss of activity seems to be (b) (4)

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The Applicant implemented changes to the sterile-fill manufacturing process in May 2011, aimed at decreasing the drug product degradation during the manufacturing process. The changes were found acceptable from the GMP point of view during inspection at the manufacturing site in Totowa, NJ, which resulted in AC recommendation on Feb 7, 2012.

In summary, the requested 12 month expiry period for the drug product is supported by the submitted data and the proposed acceptance criteria (refer to page 22 of this review). However, any further extension of the expiry period has to be limited to a prior-approval supplemental application due to the pending issues with changes in responsibilities regarding the FRBAT method and considering the recent changes in the manufacturing process with only limited amount of stability data available at this time.

- Sterile Fill Manufacturing of the Drug Product

The drug product is manufactured in a (b) (4) manufacturing facility in Totowa, NJ. The last reported change to the process was in May 2011. The recent GMP inspection of the facility yielded AC status as of Feb 7, 2012, and the Microbiology review consult dated Feb 7, 2012, recommends acceptable status. In addition, the prior GMP inspection at this site (Sep 17, 2008) recommended Acceptable GMP status for the NDA approval.

Originally, the drug product manufacturing process was burdened with multiple GMP shortcomings and none of the subsequent drug product manufacturing facilities (b) (4), Laureate Pharma and Discovery) was able to assure an acceptable GMP status until Sep 2008, despite several inspections at each site. The original manufacturing site, (b) (4) (clinical batches) was changed to the Laureate Pharma Totowa, NJ site (NDA batches) during the last phase of the IND development. Subsequently, multiple changes to the drug product manufacturing process and change to the container closure stopper were implemented at the Totowa site, which was purchased by the Applicant, Discovery Labs. During the NDA review, multiple media fill failures and numerous drug product batch failures of acceptance criteria for sterility and/or biological activity at 6, 12 and 18 months of testing were observed. Also, each of the six GMP inspections resulted in the issuance of FDA Form 483, noting serious GMP violations. All of the Microbiology and GMP deficiencies were corrected in the fourth review cycle and the current status is also AC.

- Drug Product Specifications

The last version of the Drug Product Specifications (Revision 8) is dated Jan 13, 2012, and it was submitted in an amendment dated Jan 16, 2012, in response to our IR letter dated Dec 23, 2011 (refer to page 22 of this review). The proposed acceptance criteria for (b) (4) impurities, biological

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activity, surface tension, viscosity, particle size distribution, foreign particulate matter and volume in container were revised to reflect results for drug product batches representative of the to-be-marketed product.

The original NDA application was submitted with inadequate characterization and controls for the four active ingredients, lack of validated method and data for drug product biological activity and inadequate resolution and control of the drug product impurity profile, with multiple unknown and unqualified impurities substantially exceeding the ICH recommendation thresholds, i.e., in the (b) (4) range. These deficiencies were communicated to the Applicant in the 74-day Filling Letter and in subsequent twenty one IR letters issued during the five review cycles for this application.
The regulatory history of the method controlling the biological activity of drug product is described above in this Summary (II.C) and Version 2 of the method is considered adequate by the join review team of CMC, PharmTox and Statistics reviewers. In addition, refer to the summary for proposed changes to responsibilities for QA and data analysis for the FRBAT method, on page 19 of this review.

The resolution of the qualification issues for about twenty identified and several unidentified impurities in the drug product required extensive collaboration and multiple meetings between the CMC and Pharmacology and Toxicology review teams and was successfully accomplished in the previous (fourth) review cycle.
The controls for APIs, and deficiencies pertaining to the specification attributes controlling the physicochemical properties of drug product are adequately resolved as of conclusion of this review. Refer to Drug Substance and Drug Product Specification sections of this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Eugenia Nashed, Ph.D. 3/2/12
ChemistryTeamLeaderName/Date: Alan Schroeder, Ph.D. 3/x/12
Branch Chief, ONDQA: Prasad Peri/Refer to DARRTS stamp date

C. CC Block

10 PAGES HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

Reference ID: 3096671

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EUGENIA M NASHED
03/05/2012

PRASAD PERI
03/05/2012
I concur

NDA 21-746

Surfaxin (lucinactant) Intratracheal Suspension

Discovery Laboratories, Inc.

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division III, Branch 8

for

Division of Pulmonary, Allergy and Rheumatology Products

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Chemistry Review Data Sheet

1. NDA 21-746

2. REVIEW # 5

3. REVIEW DATE: 8-February-2012

4. REVIEWER: Eugenia M. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Submissions Reviewed Previously (Review cycles 1-4)	Document Date	CDER Date	Assigned Date
Original **NDA**	13-Apr-2004	15-Apr-2004	26-Apr-2004
Amendment	29-Jun-2004	30-Jun-2004	12-Jul-2004
Amendment	13-Sep-2004	14-Sep-2004	16-Sep-2004
Amendment	19-Oct-2004	20-Oct-2004	25-Oct-2004
Amendment	15-Nov-2004	16-Nov-2004	24-Nov-2004
Amendment	23-Nov-2004	26-Nov-2004	13-Dec-2004
Amendment	04-Jan-2005	05-Jan-2005	10-Jan-2005
Amendment	06-Jan-2005	10-Jan-2005	18-Jan-2005
Amendment **AZ**	05-Oct-2005	11-Oct-2005	19-Oct-2005
Amendment BC	20-Jan-2006	24-Jan-2006	25-Jan-2006
Amendment **AZ**	31-Oct-2007	01-Nov-2007	19-Nov-2007
Amendment BC	05-Dec-2007	06-Dec-2007	17-Dec-2007
Amendment BC	07-Dec-2007	10-Dec-2007	23-Dec-2007
Amendment BC	20-Dec-2007	20-Dec-2007	10-Jan-2008
Amendment BC	21-Dec-2007	26-Dec-2007	10-Jan-2008
Amendment BC	18-Jan-2008	23-Jan-2008	11-Feb-2008
Amendment BC	29-Feb-2008	29-Feb-2008	13-Mar-2008
Amendment **AZ**	17-Oct-2008	20-Oct-2008	28-Oct -2008
Amendment BC	12-Feb-2009	13-Feb-2009	18-Feb-2009

6. SUBMISSIONS BEING REVIEWED:

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Submissions Reviewed	Document Date	CDER Date	Received Date
Amendment **AZ**	02-Sep-2011	06-Sep-2011	15-Sep-2011
Amendment BC	10-Oct-2011	11-Oct-2011	16-Oct-2011
Amendment BC	14-Nov-2011	15-Nov-2011	21-Nov-2011
Amendment BZ	16-Jan-2012	17-Jan-2012	25-Jan-2012
Amendment BZ	19-Jan-2012	20-Jan-2012	02-Feb-2012
Amendment BZ	23-Jan-2012	24-Jan-2012	30-Jan-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Discovery Laboratories, Inc.

Address: 2600 Kelly Road, Suite 100, Warrington, PA 18976-3622

Representative: Russell G. Clayton Sr., Senior Vice President., Research and Development Tel.: 215-488-9470

1. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Surfaxin

b) Non-Proprietary Name (USAN): Lucinactant Intratracheal Suspension

c) Code Name/# (ONDC only): KL_4

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

2. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Lung surfactant for premature infants

11. DOSAGE FORM: Intratracheal Suspension, 5.8 mL/kg body weight

12. STRENGTH/POTENCY: 0.862 mg/mL sinapultide, 22.5 mg/mL DPPC, 7.5 mg/mL POPG and 4.05 mg/mL PA.

13. ROUTE OF ADMINISTRATION: Intratracheal

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14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

There are four active pharmaceutical ingredients (APIs) in this drug product: 21-aa synthetic peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA). Together they form an active structure of lucinactant.

- **Sinapultide** - New Molecular Entity (NME)

L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine.

CAS 138531-07-4
Molecular formula: $C_{126}H_{239}N_{26}O_{22}$
Molecular weight: 2470

- **DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)**

CAS 63-89-8
Molecular formula: $C_{40}H_{80}NO_8P$
Molecular weight: 734.05

- **POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol) sodium**

CAS 13879-80-6
Molecular formula: $C_{40}H_{76}NPO_{10}Na$
Molecular weight: 771.00

- **PA (palmitic acid; hexadecanoic acid)**

CAS 57-10-3
Molecular formula: $C_{16}H_{32}O_2$

Reference ID: 3086371

Molecular weight: 256.42

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	COD E[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	ADEQUATE Inadequate Inadequate	Rev #3: 11/3/05 Suong T. Tran Rev #2: 10/7/04 Rev #1: 7/9/04	The updates to the DMFs provided after the review date do not contain any changes or data that would warrant the Adequate status indication for this DMF. Originally, 23 deficiencies were forwarded to the holder. Second review listed 7 remaining deficiencies. Review #3 yielded an Adequate status.
	II			1	ADEQUATE Inadequate Inadequate	1/26/12 Art Shaw 3/1/06 Eugenia Nashed 1/18/05 Edwin Jao	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet. Originally, the DMF lacked adequate specifications for impurities and sufficient stability data.
	II				ADEQUATE	1/26/12 Art Shaw	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet
(b) (4)	II	(b) (4)	(b) (4)	1	ADEQUATE IR letter pending	1/26/12 Art Shaw 4/15/08 Art Shaw	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet. Originally, the DMF contained inadequate impurity profile and stab. Data, but the issues are resolved.
	II			1	ADEQUATE IR letter pending Inadequate	1/26/12 Art Shaw 3/28/08 Art Shaw 1/19/05 Art Shaw	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet. Originally, the DMF contained inadequate impurity

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							profile and stab. Data, but the issues are resolved.
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate Adequate Inadequate Inadequate	1/26/12 Art Shaw 3/20/08 Art Shaw 3/2/06 Eugenia Nashed 1/14/05 Edwin Jao	E-mail statement from Dr. Shaw, the review is not filed to DARRTS yet. Originally, the DMF contained inadequate impurity profile and stab. Data, but the issues are resolved.
(b) (4)				1	DMF WITHDRAWN Inadequate Inadequate	3/7/06 Vinayak Pawar 1/18/05 Vinayak Pawar	The applicant purchased the manufacturing facility and became the new owner (1/06) of the DMF. DMF was withdrawn from the application on Oct 31, 2007. Two previous reviews of the DMF identified number of serious deficiencies.
(b) (4)				5	Not reviewed		Type I DMF. Facility is no longer involved in the drug manufacturing or testing.
(b) (4)	III	(b) (4)	(b) (4)	1	ADEQUATE	11/10/10 Joel Hathaway	
	III			1	ADEQUATE	9/18/11 Kristen Anderson	Also, adequate for similar formulation Rev 8/26/03 by J. Salemme, HFD-580.
	III				ADEQUATE	9/27/11 Marla Stevens Riley	Microbiology evalauation

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

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7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 40,287 (b) (4)	Discovery Laboratories	Surfaxin Intratracheal Suspension	Active	N/A	IND drug product batches were manufactured at the (b) (4) site, which has "WITHHOLD" recommendation due to the multiple GMP violations (several inspections).

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EER	GMP compliance for DS and DP manufacturing and testing sites	EER update resubmitted Oct 2011 EER update resubmitted in Nov 2007 EER update resubmitted in Nov 2005 5/11/04	Jan 25, 2012: PENDING Sep 17, 2008: ACCEPTABLE May 2008: Withhold Approval Apr 2006: Withhold Approval Feb 2006: Withhold Approval Oct 2005: Withhold Approval Feb 2005: Withhold Approval	The drug product manufacturing site in Totowa, NJ was re-inspected in Jan 2012, to evaluate the manufacturing changes implemented in May 2011, to the sterile fill process. The evaluation of the inspection is pending as of conclusion date of this review. The GMP inspection in Apr 2008, at the drug product manufacturing facility (Totowa, NJ) resulted in Acceptable recommendation in Sep 2008, after adequate correction of deficiencies noted in Form 483. All five prior inspections identified serious GMP deficiencies at this sterile fill manufacturing site (Totowa, NJ). Also, the prior manufacturing site for clinical batches at (b) (4) received several FDA Forms 483 and was not able to secure an acceptable recommendation from the ORA.
---	---	---	---	---
GLP	GLP compliance of the testing in premature rabbits. Execution and validation of the method for testing Biological Activity	10/2011 (DPARP) and second part of inspection	Jan 25, 2012: PENDING Dec 16, 2011: EER with seven GLP deficiencies was issued	The GLP/GMP evaluation of the Warrington, PA Discovery site is pending, with inspection to complete by Feb 24, 2012. The Agency learned that this site is also involved in the biological activity testing as a result of the inspection at the (b) (4) . The previous GMP inspection at the

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	of the drug product (FRBAT method)	01/2012 (DPARP)	for (b) (4) site.	Warrington site (Dec 2011) has AC recommendation. DPARP requested a GLP evaluation of the testing performed in premature rabbits, since the method is pivotal for linking the efficacy of the currently manufactured drug product to the drug product used in clinical trials. The same method is used in the release and stability testing of the drug product. The inspection performed at the (b) (4) testing site revealed serious GLP violations and the fact that part of the method is performed at another facility, Discovery Laboratories at Warrington, PA (Raw data analysis, interpretation, and reporting). An inspection of this facility was requested by DPARP. The status of the GLP inspection is indicated as VAI (voluntary action indicated) and the evaluation of the GMP part of the inspection is under evaluation by the OC. The Applicants responses to the Form 483 deficiencies are being evaluated.
Pharm/Tox	1) Appropriateness of the method testing biological activity of the drug product in premature rabbits. The method is used for efficacy linking of the currently manufactured drug product to the product used in clinical studies. Also, it is used as a regulatory release and stability testing method for the drug product. 2) Qualification of impurities in drug substance and drug product.	09/2012 11/2008 10/19/06 11/15/05 05/2004 09/2012 05/2004	<u>Current Status</u>: PENDING <u>Prior Review Cycles:</u> Inadequate 3/4/09, Luqi Pei Inadequate 3/11/08, Huiqing Hao Inadequate 3/3/06, Huiqing Hao Inadequate 12/01/04, Huiqing Hao <u>Current Status</u>: ADEQUATE 12/12/11, Luqi Pei Inadequate in the prior five review cycles.	The scientific merits of the proposed method are considered adequate (Review dated 12/12/11 by Dr. Luqi Pei). However, the review of the method validation and on site GLP audit are pending as of completion date of this review. Any PharmTox comments resulting from the pending evaluation will be forwarded to the applicant and may impact the nature of recommended action. All issues pertaining to the qualification of drug substance and drug product impurities are adequately resolved in this review cycle – refer to PharmTox review dated 12/12/11.
Biopharm	N/A			

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Methods Validation				No MV deem necessary at this point.
Division Of Medication Error Prevention and Analysis	Assessment of the proposed proprietary name	7/16/04	Current Status: AC 01/24/12 Carol Holquist Prior Review Cycles: Inadequate Inadequate Denise Toyer 3/1/06 Inadequate Denise Toyer 11/8/04	Acceptable Name acceptable from promotional perspective. NOT RECOMMENDED due to sound-like and look-like similarities with other drug names. The name Surfaxin is NOT RECOMMENDED + labeling comments concerning safety
DDMAC	Adequacy of PI	7/16/04	PENDING Inadequate Jialynn Wang 10/18/04	Label needs minor revisions
EA	Exclusion requested	N/A	Acceptable	See CMC review #1
Microbiology	Sterile manufacture, fill and testing of the drug product.	10/2011 5/10/04	Current Status: Acceptable Prior Review Cycles: Adequate Inadequate 3/7/06, V. Pawar Inadequate 1/18/05, V. Pawar	Review dated Feb 7, 2012, is in DARRTS.

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The Chemistry Review for NDA 21-746

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC review team recommends an APPROVAL action for this NDA, pending satisfactory recommendations from the Pharmacology and Toxicology team (review and data audit for the method testing drug product biological activity in premature rabbits is pending), and an Acceptable recommendation from the ORA (GMP inspections of the drug product manufacturing site, GMP inspection of drug substance manufacturing site in (b) (4) and GLP/GMP inspections for two sites testing the biological activity of the drug product are pending). The final recommendation will be outlined in an amended CMC review to be placed in DARRTS after completion of pending consult reviews and pending GMP/GLP inspections.

The requested expiry period for the drug product is 12 months and it is supported by the submitted data. The expiry period may be extended only *via* a prior-approval (PA) supplemental application with adequate supporting stability data due to the due to the observed instability of the formulation (refer to Section II. C, of the Summary below), recent changes to the manufacturing process and pending compliance issues regarding the *in vivo* rabbit method for testing drug product biological activity (FRBAT).

This NDA was submitted in April 2004, and was burdened with serious manufacturing shortcomings and control deficiencies. After four review cycles and numerous meetings with the Applicant providing regulatory guidance and advice, the majority of the manufacturing issues seem resolved, however a GMP inspection evaluating the 2011-implemented changes to the sterile fill process is pending as of conclusion date of this review. In addition, possibly serious deficiencies were noted during the GLP inspection at the (b) (4) site, where the testing for biological activity (FRBAT) of the drug product is performed (refer to Pharmacologist review by Charles Bonapace dated 01/13/12). The second part of the GLP inspection at the Warrington, PA Discovery site responsible for the raw data processing, reporting, interpretation and method validation for FRBAT testing is currently pending. The Agency learned about the involvement of the Discovery site only during the inspection at the (b) (4) site and the second part of the inspection was requested due to the high impact of this method. The importance of the analytical method evaluating the biological activity of the drug product (assessing drug potency in premature rabbits, FRBAT) is paramount for this application and possibly has significant bearing on

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the approvability of this NDA. It serves as a regulatory release and stability method for the drug product and it is pivotal for linking the efficacy of the currently manufactured drug product to the clinical drug product batches. The method was not in use during clinical trials and was considered inadequate during prior review cycles. Refer to pending reviews by the Medical review team and Pharmacology and Toxicology review team linking the FRBAT method to studies in premature lambs which were done concurrently with the clinical program using the clinical batches of drug product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None, at this point.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This is a complex drug product (lucinactant) where several active ingredients need to (b) (4). It consists of an aqueous suspension (b) (4) of a synthetic, 21-amino acid peptide (sinapultide), dipalmitoyl-phosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium (POPG, Na) and palmitic acid (PA). The amino acid sequence of sinapultide peptide comprises four repeating units made of one lysine and four leucines (KL_4). It is a New Molecular Entity (NME) and it is designed to (b) (4) simulate the nature of the structure characteristic for the lung surfactant protein B (SP-B). (b) (4)

The combination of these four active ingredients was designed to mimic the behavior of the *in vivo* lung surfactant system responsible for lowering surface tension in the lungs of premature infants. The biological activity of the drug product (lucinactant) (b) (4) is controlled by the testing of lung function in premature rabbits (FRBAT test).

There are four active ingredients in this drug product: 21-amino acid peptide (sinapultide), two phospholipids (DPPC and POPG, Na), and palmitic acid (PA). Each API is supported and by a corresponding DMF and controlled by the acceptance criteria specifications. The current status is "Adequate" for each DMF – refer to the "Supporting DMFs" table above in this review.

The drug product suspension is manufactured by a sterile-fill process by (b) (4)

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(b) (4)

The final concentration is adjusted to 0.862 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG, Na (30 mg/mL of total phospholipids) and 4.05 mg/mL of PA. The pH of the suspension is 7.4. The nominal fill per vial is 8.5 mL, (b) (4) The drug product forms a gel-like white suspension in room temperature and needs to be warmed up to 40ºC, to achieve a free flowing consistency before the administration. It is administered in a hospital setting via intratracheal tube and the recommended dose is 5.8 mL per kg body weight of the infant.

B. Description of How the Drug Product is Intended to be Used

Surfaxin (lucinactant) Intratracheal Suspension is intended for the prevention of Respiratory Distress Syndrome (RDS) in premature infants. It is a milky-white suspension intended for an intratracheal instillation to the lungs of premature neonates in a hospital setting. The recommended dose for Surfaxin is 5.8 mL/kg body weight for up to four doses in the first 48 hours of life. The exact dose for administration is determined by the attending physician based on the weight of the neonate. The recommended dosing chart is included in the package insert.

The nominal fill is 8.5 mL of drug product suspension per 10 mL sterile vial to be stored at 5°C ± 3 °C (refrigerator). Before the use, the suspension needs to be warmed up by placing the vial in a dry block heater set at 44°C (111°F) for 15 minutes. The warmed drug product has to be used within 2 hours of removing from the refrigerator. Vials are for single use only and any unused portion of the drug has to be disposed.

C. Basis for Approvability or Not-Approval Recommendation

This application is considered approvable from the CMC perspective pending satisfactory recommendation from the Pharmacology and Toxicology team (evaluation of the FRBAT method for drug product biological activity in premature rabbits, with GLP/GMP inspections pending), and an acceptable recommendation from the ORA (pending GMP inspection at the manufacturing site and GLP inspection at the testing site).

The status of major review issues emphasized during this review cycle to support the CMC recommendation is summarized below.

- Biological Activity (Potency) of the Drug Product

The potency of this complex drug product mixture is tested in premature rabbits (FRBAT method) by assessing the lung function (respiratory system compliance,

Reference ID: 3086371

C_{RS} = $\Delta V/\Delta P$) after instillation of the drug product and in comparison to the negative and positive (approved lung surfactant) controls. The FRBAT method is used for bridging the activity of the currently manufactured drug product to the drug product used in clinical trials and also as a release and stability testing method. The original NDA application has lacked an adequately validated method and data for drug product biological activity and the method was considered inadequate after four review cycles, despite several feedback letters and multiple meetings with the Applicant. Refer to Pharmacology and Toxicology reviews dated Mar 4, 2009, by Dr. Luqi Pei, and Mar 11, 2008, by Dr. Huiqing Hao.
In this review cycle a team comprised of the Pharmacology and Toxicology reviewer, the Statistics reviewer and this reviewer worked closely with the Applicant for several months by reviewing in depth submissions provided to IND 40,287, associated with this NDA, with subsequent versions of the method and method validation corrected based on our feedback comments, and finally reviewing the complete response to the NDA. Based on the submitted data the Version 2 of the method's validation seems acceptable to our team. However, after the GLP inspection at the rabbit testing site (b) (4) the investigator noted that part of the method (raw data processing, data evaluation and reporting, and method validation) is performed at a different site (Discovery site at Warrington, PA) and the data integrity can not be assured without a second inspection tracking the data and their processing. In addition, a multiple GLP deficiencies were reported on FDA form 483 for the (b) (4) site. The method was changed and version 5 of the method seems to be currently in use. The DPARP requested a follow up directed GLP inspection to complete the data tracking since the FRBAT method is pivotal for bridging the efficacy of the drug product and establishing adequate drug product controls. The outcome of this inspection may have considerable bearing on the approvability of this NDA. An additional CMC review addendum will be placed in DARRTS after completion of the pending consult reviews and pending GMP/GLP inspections.

- Limited Drug Product Stability

From the CMC perspective the most serious concern pertains to the limited stability of the drug product due to (b) (4) and decreases the biological activity of the drug product. A substantial decline in the biological activity (*ca* 25% decrease over 12 months) and an increase in the surface tension is noted during the storage in refrigerator (Labeled storage conditions). (b) (4)
The Applicant implemented changes to the sterile-fill manufacturing process in

Reference ID: 3086371

May 2011, aimed at decreasing the drug product degradation during the manufacturing process. The evaluation of these changes is pending by the Microbiology review team and by the FDA Investigators during the currently ongoing GMP inspection at the manufacturing site in Totowa, NJ.

In summary, the requested 12 month expiry period for the drug product is supported by the submitted data and the proposed acceptance criteria (refer to a detailed evaluation in the Drug Product Specifications section of this review). However, any further extension of the expiry period has to be limited to a prior-approval supplemental application due to the pending issues with FRBAT method and recent changes in the manufacturing process with only a limited amount of stability data available at this time.

- Sterile Fill Manufacturing of the Drug Product

The drug product is manufactured in a (b) (4) manufacturing facility in Totowa, NJ. The last reported change to the process was in May 2011. Currently, the GMP inspection of the facility is ongoing and the Microbiology review consult dated Feb 7, 2012, recommends acceptable status. The prior GMP inspection at this site (Sep 17, 2008) recommended Acceptable GMP status for the approval.

Originally, the drug product manufacturing process was burdened with multiple GMP shortcomings and none of the subsequent drug product manufacturing facilities (b) (4) Laureate Pharma and Discovery) was able to assure an acceptable GMP status until Sep 2008, despite several inspections at each site. The original manufacturing site, (b) (4) (clinical batches) was changed to the Laureate Pharma Totowa, NJ site (NDA batches) during the last phase of the IND development. Subsequently, multiple changes to the drug product manufacturing process and change to the container closure stopper were implemented at the Totowa site, which was purchased by the Applicant, Discovery Labs. During the NDA review, multiple media fill failures and numerous drug product batch failures of acceptance criteria for sterility and/or biological activity at 6, 12 and 18 months of testing were observed. Also, each of the six GMP inspections resulted in the issuance of FDA Form 483, noting serious GMP violations. All of the Microbiology and GMP deficiencies were corrected in the last review cycle. The evaluation of the recent manufacturing changes by the GMP Inspection team is pending as of the conclusion date of this review.

- Drug Product Specifications

The last version of the Drug Product Specifications (Revision 8) is dated Jan 13, 2012, and it was submitted in an amendment dated Jan 16, 2012, in response to

Reference ID: 3086371

our IR letter dated Dec 23, 2011. The proposed acceptance criteria for (b) (4) impurities, biological activity, surface tension, viscosity, particle size distribution, foreign particulate matter and volume in container were revised to reflect results for drug product batches representative of the to-be-marketed product.

The original NDA application was submitted with inadequate characterization and controls for the drug substance (four active ingredients), lack of validated method and data for drug product biological activity and inadequate resolution and control of the drug product impurity profile, with multiple unknown and unqualified impurities substantially exceeding the ICH recommendation thresholds, i.e., in the (b) (4) range. These deficiencies were communicated to the Applicant in the 74-day Filling Letter and in subsequent twenty one IR letters issued during the five review cycles for this application.

The regulatory history of the method controlling the biological activity of drug product is described above in this Summary (II.C) and Version 2 of the method is considered adequate by the joined review team of CMC, PharmTox and Statistics reviewers. Subsequent changes to the method and method validation by the Pharmacology and Toxicology team is pending. The evaluation of data transfer between two testing site and subsequent computations is pending by the GLP Investigator as of conclusion date of this review.

The resolution of the qualification issues for about twenty identified and several unidentified impurities in the drug product required extensive collaboration and multiple meetings between the CMC and Pharmacology and Toxicology review teams and was successfully accomplished in the last review cycle.

The controls for APIs, and deficiencies pertaining to the specification attributes controlling the physicochemical properties of drug product are adequately resolved as of conclusion of this review. Refer to Drug Substance and Drug Product Specification sections of this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Eugenia Nashed, Ph.D. 2/8/12
ChemistryTeamLeaderName/Date: Alan Schroeder, Ph.D. 2/8/12
Branch Chief, ONDQA: Prasad Peri/Refer to DARRTS stamp date

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Reference ID: 3086371

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/s/

EUGENIA M NASHED
02/11/2012

PRASAD PERI
02/13/2012
I concur

NDA 21-746

Surfaxin (lucinactant) Intratracheal Suspension

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Discovery Laboratories, Inc.
2600 Kelly Road, Suite 100,
Warrington, PA 18976-3622

Indication: **P**revention and rescue of respiratory distress syndrome (RDS) in premature infants.

Presentation: The drug product suspension is sterile-filled to 10 mL sterile glass vials and contains 0.862 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG and 4.05 mg/mL of PA, total 8.5 mL per vial. This corresponds to a concentration of 0.862 mg of peptide and 30 mg of total phospholipids per 1 mL of drug product suspension.

EER Status: Acceptable

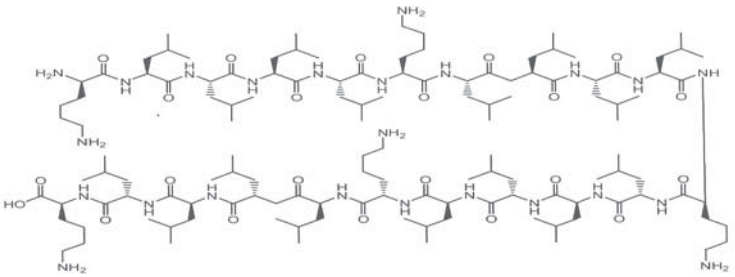
Consults:	EA –	Categorical exclusion provided
	Statistics –	N/A
	Methods Validation –	Not recommended
	Biopharm–	N/A
	Microbiology –	Acceptable
	Pharm/toxicology –	Inadequate

Original Submission:	13-April-2004
Re-submissions:	Yes (see amendments listed in CMC reviews)
Post-Approval CMC Agreements:	None beyond the typical stability commitment.

Background:
This NDA was submitted in April 2004; the drug product has an orphan drug designation since 10/18/95; AN 95-913.
It is important to report here that, since 2004 and after four review cycles; the NDA still has outstanding and unresolved issues related to the inadequate method for testing biological activity and inadequate qualification of impurities as outlined in the Pharm. Tox. Review. These outstanding issues have a direct impact on the overall quality of the drug product.

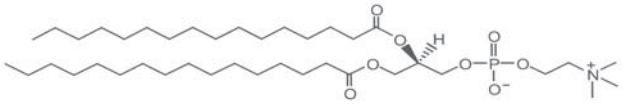
Drug Substance:
There are four active pharmaceutical ingredients (APIs) in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

– **Sinapultide**
L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-Llysyl-
L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine. Chemical Structure



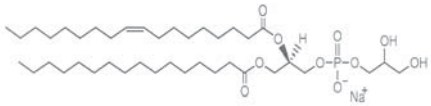
Molecular formula: $C_{126}H_{239}N_{26}O_{22;}$ Molecular weight: 2470

– **DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)** Chemical Structure



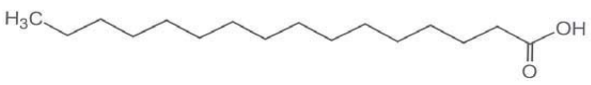
Molecular formula: $C_{40}H_{80}NO_8P$; Molecular weight: 734.05

– **POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)** Chemical Structure



Molecular formula: $C_{40}H_{76}NPO_{10}Na$; Molecular weight: 771.00

– **PA (palmitic acid; hexadecanoic acid)** Chemical Structure



Molecular formula: $C_{16}H_{32}O_{2;}$ Molecular weight: 256.42

CMC information related to each of the above APIs is supported by the corresponding Drug Master File. All Drug Master Files (DMFs) associated with the drug substances were reviewed and found acceptable.

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product is manufactured by [redacted] The drug product suspension [redacted] nominal fill) is aseptically and packaged into a sterile 10 mL glass vial (USP Type I [redacted] glass) sealed with [redacted] gray rubber stopper and red flip-off aluminum seal.

Specifications for SURFAXIN (lucinactant) include: appearance; identification of four active ingredients; assay of four active ingredients; impurities [redacted] pH; surface tension; *in vivo* activity; viscosity; sterility; bacterial endotoxins; particulates; and particle size.

The drug product consists of an aqueous suspension [redacted] of a synthetic, 21-amino acid peptide (sinapultide), dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG) and palmitic acid (PA). The amino acid sequence of the sinapultide (KL_4) was designed to simulate the nature of the structure of the lung surfactant protein B (SP-B). However, it is noted that the [redacted] to mimic the behavior of the *in vivo* system responsible for lowering surface tension in the lungs.

The drug product suspension is sterile-filled to 10 mL sterile glass vials and contains 0.862 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG and 4.05 mg/mL of PA, total 8.5 mL per vial. This corresponds to a concentration of 0.862 mg of peptide and 30 mg of total phospholipids per 1 mL of drug product suspension.

Surfaxin (lucinactant) Intratracheal Suspension is intended for the prevention and rescue of respiratory distress syndrome (RDS) in premature infants. It is a milkywhite suspension intended for an intratracheal instillation to the lungs of premature neonates in a hospital setting. The proposed dose for Surfaxin is 5.8 mL/kg body weight/dose (5.0 mg of peptide and 174 mg phospholipids/kg body weight) for up to four doses in the first 48 hours of life. The exact administered dose is determined by the attending physician based on the weight of the neonate.

The nominal fill is 8.5 mL of suspension per 10 mL sterile vial to be stored at 5°C ± 3 °C (refrigerator). Before the use, the suspension needs to be warmed up by placing the vial in a dry block heater set at 44°C (111°F) for 15 minutes. The warmed drug product has to be used within 2 hours of warming. Vials are for single use only and any unused portion of the drug has to be discarded.

The submitted stability data support the requested expiry period of 12 months for the currently manufactured drug product, when stored at 2-8°C.

Conclusion: Drug product is satisfactory.

Overall Conclusion:
From a CMC perspective, the application is approvable pending satisfactory responses to PHARM. TOX. deficiencies (inadequate method for testing biological activity and inadequate qualification of impurities).

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Ali Al-Hakim

4/13/2009 10:49:08 PM

CHEMIST

Addendum to P/T Chemistry Consult Review No. 5

NDA No.: 21-746 (Resubmission of October 17, 2008)
Sponsor: Discovery Laboratories
Drug Product: Surfaxin (lucinactant) intratracheal instillation suspension

Reviewer: Luqi Pei, Ph.D.
Completion date: April 13, 2009

RE: Addendum to P/T Chemistry Consult Review No. 5

The following table will replace Table 8 (page 12) of the Chemistry Consultation Review No. 5 completed by Dr. Luqi Pei on March 4, 2009.

Table 8 Effect of Expiry Status on Lucinactant Efficacy in Pre-Term Lambs

Lot No./ Grouped	Manu-facturing Date	Time of Testing	Expiry status at Time of Testing	Mean Lung Compliance	
				Percent of Baseline	Net Increase [a]
T7002 T7003	1/23/07 1/31/07	Jul-2008	Yes	163.4 ± 15.0%	63% [b]
T7002 T7003	1/23/07 1/31/07	Sep-2007 [c]	No	226.3 ± 70.3% [d]	126%
T8004 T8005 T8006	5/21/08 7/16/08 7/31/08	Jul - Aug 2008	No	227 ± 14.4%	127% [b]
N/A	N/A	Literature	No	262.5% [e]	162.5%

a. Derived by subtracting 100 from the percent of baseline values.
b. Source: Table 7, page 11 of the current review.
c. Report date. The report did not provide the experiment date.
d. Source: Vol. 1, p 154 of the 17-OCT-2008 supplement submission.
e. Reported by Gastiasoro-Cuesta et al. (Pediatrics, 117:295-303, 2006).

In addition, the second paragraph of page 12 should be replaced by the following:

The report compared the magnitude of changes associated with the same lots (Lots T7002 and T7003) of lucinactant treatment previously reported in year 2007 and literature. Table 8 presents the results. There was a significant decrease in potency of the lots between the 2008 and previous values studies. Specifically, the mean increase in the lung compliance for Lots T7002 and T7003 was 126% and 63% when the lots were unexpired (2007) and expired (2008), respectively. This finding has significant implications to the interpretation of the rabbit model data (see the discussion and evaluation).

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/s/

Luqi Pei
4/14/2009 09:58:25 AM
PHARMACOLOGIST

Timothy Robison
4/14/2009 10:04:47 AM
PHARMACOLOGIST
I concur

INTEROFFICE MEMO

TO: NDA 21-746 (Surfaxin)
Resubmission dated October 17, 2008

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Senior Pharmacology/Toxicology Reviewer
Division of Pulmonary and Allergy Products

DATE: March 16, 2009

RE: Chemistry Consultation Review No. 5 from Dr. Luqi Pei to Dr. Jean Nashed

I concur with Dr. Luqi Pei's Review regarding the validity of an in vivo biological activity assay for assessing lucinactant potency and release specifications.

The sponsor has proposed to use an efficacy model with rabbit fetuses for assessing the potency of lucinactant batches prior to release. The Agency requested studies in the lamb model to provide a linkage between the clinical data and the rabbit model. The fetal rabbit assay was unable to differentiate lucinactant activity between expired and unexpired batches. In contrast, the preterm lamb model was able to distinguish effects of expiry status on lucinactant efficacy (i.e., the expired lucinactant lots possessed lower activity as compared to unexpired lots). Thus, the sponsor failed to establish a link between the rabbit and lamb assays as well as to the clinical data.

Lucinactant had inferior potency in improving lung compliance and acceptance criteria than beractant (positive control) in rabbit fetuses.

Dr. Pei's review offers a number of paths forward for the sponsor to address these deficiencies.

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/s/

Timothy Robison
3/16/2009 05:51:58 PM
PHARMACOLOGIST

NDA 21-746

Surfaxin (lucinactant) Intratracheal Suspension

Discovery Laboratories, Inc.

Eugenia Nashed
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA 21-746

2. REVIEW #: 4

3. REVIEW DATE: 10-March-2009

4. REVIEWER: Eugenia Nashed

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	CDER Date	Assigned Date
Original NDA	13-Apr-2004	15-Apr-2004	26-Apr-2004
Amendment	29-Jun-2004	30-Jun-2004	12-Jul-2004
Amendment	13-Sep-2004	14-Sep-2004	16-Sep-2004
Amendment	19-Oct-2004	20-Oct-2004	25-Oct-2004
Amendment	15-Nov-2004	16-Nov-2004	24-Nov-2004
Amendment	23-Nov-2004	26-Nov-2004	13-Dec-2004
Amendment	04-Jan-2005	05-Jan-2005	10-Jan-2005
Amendment	06-Jan-2005	10-Jan-2005	18-Jan-2005
Amendment AZ	05-Oct-2005	11-Oct-2005	19-Oct-2005
Amendment BC	20-Jan-2006	24-Jan-2006	25-Jan-2006
Amendment AZ	31-Oct-2007	01-Nov-2007	19-Nov-2007
Amendment BC	05-Dec-2007	06-Dec-2007	17-Dec-2007
Amendment BC	07-Dec-2007	10-Dec-2007	23-Dec-2007
Amendment BC	20-Dec-2007	20-Dec-2007	10-Jan-2008
Amendment BC	21-Dec-2007	26-Dec-2007	10-Jan-2008
Amendment BC	18-Jan-2008	23-Jan-2008	11-Feb-2008
Amendment BC	29-Feb-2008	29-Feb-2008	13-Mar-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	CDER Date	Assigned Date
Amendment AZ	17-Oct-2008	20-Oct-2008	28-Oct -2008
Amendment BC	12-Feb-2009	13-Feb-2009	18-Feb-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Discovery Laboratories, Inc.

Address: 2600 Kelly Road, Suite 100, Warrington, PA 18976-3622

Representative: Marjorie Hurley, Pharm.D., Vice President., Reg. Affairs

1. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Surfaxin

b) Non-Proprietary Name (USAN): Lucinactant Intratracheal Suspension

c) Code Name/# (ONDC only): KL_4

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

2. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Lung surfactant for premature infants

11. DOSAGE FORM: Intratracheal Suspension, 5.8 mL/kg body weight

12. STRENGTH/POTENCY: 0.862 mg/mL sinapultide, 22.5 mg/mL DPPC, 7.5 mg/mL POPG and 4.05 mg/mL PA.

13. ROUTE OF ADMINISTRATION: Intratracheal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

Chemistry Review Data Sheet

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

There are four active pharmaceutical ingredients (APIs) in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

- **Sinapultide**

L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine.

CAS 138531-07-4
Molecular formula: $C_{126}H_{239}N_{26}O_{22}$
Molecular weight: 2470

- **DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)**

CAS 63-89-8
Molecular formula: $C_{40}H_{80}NO_8P$
Molecular weight: 734.05

- **POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)**

CAS 13879-80-6
Molecular formula: $C_{40}H_{76}NPO_{10}Na$
Molecular weight: 771.00

- **PA (palmitic acid; hexadecanoic acid)**

CAS 57-10-3
Molecular formula: $C_{16}H_{32}O_2$
Molecular weight: 256.42

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]

Chemistry Review Data Sheet

(b) (4)	II	(b) (4)	(b) (4)	1	ADEQUATE Inadequate Inadequate	Rev #3: 11/3/05 Suong T. Tran Rev #2: 10/7/04 Rev #1: 7/9/04	Originally, 23 deficiencies were forwarded to the holder. Second review listed 7 remaining deficiencies. Review #3 yielded an Adequate status.
	II			1	ADEQUATE Inadequate Inadequate	3/28/08 Art Shaw 3/1/06 Eugenia Nashed 1/18/05 Edwin Jao	Lack of adequate specifications for impurities and lack of stability data.
	II			1	ADEQUATE IR letter pending Inadequate	2/6/06 Art Shaw 1/19/05 Art Shaw	IR letter sent to the Holder 2/9/06. Inadequate impurity profile and stab. data.
(b) (4)	II	(b) (4)	(b) (4)	1	ADEQUATE IR letter pending Inadequate	2/9/06 Art Shaw 1/19/05 Art Shaw	IR letter sent to the Holder 2/9/06. Inadequate impurity profile and stab. data.
	II			1	Adequate Inadequate Inadequate	 3/2/06 Eugenia Nashed 1/14/05 Edwin Jao	DMF retired, sent request to holder to submit update to Jan 2000 amend. Lack of adequate specs for impurities and lack of stab. data
(b) (4)				1	WITHDRAWN Inadequate Inadequate	 3/7/06 Vinayak Pawar 1/18/05 Vinayak Pawar	The applicant has purchased the manufacturing facility and became the new owner (1/06) of the DMF. DMF was withdrawn from the application on Oct 31, 2007. Two previous reviews of the DMF identified number of serious deficiencies.
(b) (4)				5	Not reviewed		Type I DMF for testing facility.

			submitted				
(b) (4)	III	(b) (4)	(b) (4)	1	ADEQUATE	3/23/04	
	III			1	ADEQUATE	10/21/99 Ravi Harapanhalli HFD-160	Also, adequate for similar formulation Rev 8/26/03 by J. Salemme, HFD-580.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 40,287 (b) (4)	Discovery Laboratories	Surfaxin Intratracheal Suspension	Active	N/A	IND drug product batches were manufactured at the (b) (4) site, which has "WITHHOLD" recommendation due to the multiple GMP violations (several inspections).

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EER	GMP compliance for DS and DP manufacturing and testing sites	Update resubmitted in Nov 2007 Update resubmitted in Nov 2005	Sep 17, 2008: ACCEPTABLE May 2008: Withhold Approval Apr 2006: Withhold Approval Feb 2006: Withhold	The GMP inspection in Apr 2008, at the drug product manufacturing facility at Totowa, NJ, resulted in Acceptable recommendation in Sep 2008, after correcting deficiencies noted in Form 483. This is the first AC recommendation for this manufacturing site. All prior inspections identified serious GMP

		5/11/04	Approval Oct 2005: Withhold Approval Feb 2005: Withhold Approval	deficiencies at the drug product manufacturing sites (this site at Totowa, NJ, and the prior manufacturing site for clinical batches at (b) (4) and resulted in FDA Forms 483.
Pharm/Tox	Appropriateness of the method testing biological activity of the drug product in premature rabbits. Qualification of impurities in drug substance and drug product.	11/2008 10/19/06 11/15/05	INADEQUATE 3/4/09, Luqi Pei Inadequate 3/11/08, Huiqing Hao Inadequate 2/14/06, Huiqing Hao Inadequate 12/01/04, Huiqing Hao INADEQUATE 3/4/09, Luqi Pei INADEQUATE 3/11/08, Huiqing Hao Inadequate 3/3/06, Huiqing Hao	PharmTox comments to be forwarded to the applicant PharmTox comments to be forwarded to the applicant
Biopharm	N/A			
Methods Validation	To be sent			Will be submitted upon review of applicant's response to the deficiencies
Division Of Medical Errors and Technical Support	Assessment of the proposed proprietary name	7/16/04	PENDING Inadequate Denise Toyer 3/1/06 Inadequate Denise Toyer 11/8/04	Name acceptable from promotional perspective. NOT RECOMMENDED due to sound-like and look-like similarities with other drug names. The name Surfaxin is NOT RECOMMENDED + labeling comments concerning safety
DDMAC	Adequacy of PI	7/16/04	PENDING Inadequate Jialynn Wang 10/18/04	Label needs minor revisions
EA	Exclusion requested	N/A	Acceptable	See CMC review #1
Microbiology	Sterile manufacture,		PENDING	Response to the prior deficiencies

	fill and testing of the drug product.	5/10/04	Inadequate 3/7/06, V. Pawar Inadequate 1/18/05, V. Pawar	is under review by the Microbiology Team. Any comments resulting from the review need to be forwarded to the Applicant.

The Chemistry Review for NDA 21-746

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC Team recommends APPROVABLE action for this NDA, pending satisfactory response to PharmTox team deficiencies (inadequate method for testing biological activity and inadequate qualification of impurities – see consult review by Dr. Luqi Pei dated Mar 4, 2009), and satisfactory response to Microbiology team deficiencies (deficient validation of the sterile fill process, review by Dr. Vinyak Pawar is pending).

An ACCEPTABLE (AC) recommendation from the Office of Compliance is available for this NDA as of Sep 17, 2008. The overall AC status for this application was confirmed by Ms. Shirnette Ferguson through e-mail dated Mar 6, 2009.

This NDA was submitted in April 2004, and after four review cycles, several serious deficiencies remains to be addressed by the applicant. Originally, the drug product manufacturing process was burdened with multiple GMP shortcomings and none of the drug product manufacturing facilities was able to assure an acceptable GMP status until Sep 17, 2008, despite several inspections at each site. The original manufacturing site, (b) (4) (clinical batches) was changed to Totowa, NJ (NDA batches) during the last phase of the IND development. Subsequently, multiple changes to the drug product manufacturing process and change to the container closure stopper were implemented at the Totowa site. During the NDA review, multiple batch failures for sterility and/or biological activity at 6, 12 and 18 months of testing were observed. Also, each of the GMP inspections resulted in FDA Form 483, noting serious GMP violations. The majority of the Microbiology and GMP deficiencies seem to be corrected at this point, although the review by the Microbiology team is pending as of the conclusion date of this review. However, the analytical method for testing biological activity of the drug product (assessing drug potency in premature rabbits) remains deficient and proved to be inadequate for bridging the drug product batches used in the clinical trials to the currently manufactured drug product. Also, the qualification of some impurities exceeding the ICH recommendation limit is considered inadequate by the PharmTox review team, e.g., (b) (4) impurity in the drug product – refer to reviews dated Mar 4, 2009, by Dr. Luqi Pei, and Mar 11, 2008, by Dr. Huiqing Hao.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product consists of an aqueous suspension (b) (4) of a synthetic, 21-amino acid peptide (sinapultide), dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG) and palmitic acid (PA). The amino acid sequence of the sinapultide (KL_4) was designed to simulate the nature of the structure of the lung surfactant protein B (SP-B). However, it is noted that the (b) (4) and to mimic the behavior of the *in vivo* system responsible for lowering surface tension in the lungs.

There are four active ingredients in this drug product: 21-amino acid peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA). Each API is supported by the corresponding DMF - see the "Supporting DMFs" table above. After several review cycles, the status is “Adequate” for each of the supporting DMFs.

The drug product suspension is sterile-filled to 10 mL sterile glass vials and contains 0.862 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG and 4.05 mg/mL of PA, total 8.5 mL per vial. This corresponds to a concentration of 0.862 mg of peptide and 30 mg of total phospholipids per 1 mL of drug product suspension.

B. Description of How the Drug Product is Intended to be Used

Surfaxin (lucinactant) Intratracheal Suspension is intended for the prevention (b) (4) of respiratory distress syndrome (RDS) in premature infants. It is a milky-white suspension intended for an intratracheal instillation to the lungs of premature neonates in a hospital setting. The proposed dose for Surfaxin is 5.8 mL/kg body weight/dose (5.0 mg of peptide and 174 mg phospholipids/kg body weight) for up to four doses in the first 48 hours of life. The exact administered dose is determined by the attending physician based on the weight of the neonate.

The nominal fill is 8.5 mL of suspension per 10 mL sterile vial to be stored at 5°C ± 3 °C (refrigerator). Before the use, the suspension needs to be warmed up by placing

the vial in a dry block heater set at 44°C (111°F) for 15 minutes. The warmed drug product has to be used within 2 hours of warming. Vials are for single use only and any unused portion of the drug has to be discarded.

C. Basis for Approvability or Not-Approval Recommendation

This application is considered APPROVABLE from the CMC perspective pending satisfactory resolution of the remaining deficiencies. The major issues include inadequate method for testing biological activity of the drug product (assessing drug potency in premature rabbits) and inadequate acceptance criteria for impurity (b) (4) (b) (4) in the drug product. The biological activity method remains deficient after four review cycles and proved to be inadequate for bridging the drug product batches used in the clinical trials to the currently manufactured drug product. Refer to PharmTox reviews dated Mar 4, 2009, by Dr. Luqi Pei, and Mar 11, 2008, by Dr. Huiqing Hao. The review of Applicant's responses to the Microbiology team deficiencies is pending, as of the conclusion date of this review.

This is the fourth review cycle for this NDA and covers applicant's submissions dated Oct. 17, 2008 (full response to May 1, 2008, letter), and Feb 12, 2009, amendment with revised drug product specifications. Upon issuing third AE letter on May 1, 2008, the Division met with the applicant (Discovery Labs) on Jun 18, 2008, to discuss serious deficiencies remaining for this application (see meeting minutes in DFS). The full response dated Oct 17, 2008, provides responses to 18 deficiencies identified by different review teams and 2 comments on the proposed labeling. The responses to Comments #1-10 are under review by the Microbiology team, and responses to Comments # 11b, #13c and #14, and the revised impurity specifications submitted in amendment dated Feb 12, 2009, have been reviewed by the PharmTox team – review dated Mar 4, 2008, by Dr. Luqi Pei.

During the NDA review, numerous serious deficiencies were identified for this application, including the potential review issues which were forwarded to the applicant in the 74-day Filling Letter dated June 25, 2004, as follow.

- Potentially serious compliance problem at the drug product manufacturing site.
- Lack of adequate stability data, contrary to our recommendation at the pre-NDA meeting on Jun 13, 2003.
- Lack of validated method and data monitoring biological activity of the drug product, contrary to our recommendation at the pre-NDA meeting on Jun 13, 2003.
- Multiple unknown and unqualified impurities (b) (4) in the drug product substantially crossing the ICH recommendations.

Subsequent review cycles for this NDA revealed additional deficiencies, including inadequate characterization and release of APIs, inadequate drug product controls, inadequate resolution of the impurity/decomposition profiles, lack of validated

analytical methods and inadequate stability data. Also, multiple drug product batch failures for sterility and/or biological activity at 6, 12 and 18 months of testing were observed. Each drug product manufacturing site (b) (4) manufacturing clinical batches, and Totowa manufacturing NDA batches), failed repeatedly to pass the GMP inspection, until Sep 2008. The above manufacturing sites were not able to assure the sterility of the manufacturing process – refer to Microbiology review #1, #2, and #3. Upon issuing second AE letter on Mar 31, 2006, the Division met with the applicant (Discovery Labs) on Dec 21, 2006, to discuss serious deficiencies remaining and to chart a possible path forward for this application (see meeting minutes in DFS). Several manufacturing process changes and a change of the container closure stopper were introduced to the drug product. Release and stability data for 3 drug product batches manufactured with the revised process at Totowa site in Jan/Feb 2007, were submitted, with a 12 month update in Mar, 2008. It was noted that these process validation drug product batches exhibit lesser variability of the release and stability data and the analytical methods have been improved, in comparison to the earlier drug product batches. However, a substantial decline in the biological activity and increase in the surface tension it noted during the storage. The (b) (4) Therefore, the requested 12 month expiry period for the drug product is barely supported, based on the submitted data and the proposed acceptance criteria.

From the CMC perspective the most serious concern pertains to the limited stability of the drug product due (b) (4) The amounts of (b) (4) impurities seem to increase substantially upon storage. The formation of these (b) (4) seem to alter (b) (4) (based on submitted Circular Dichroism data) and decreases the biological activity of the drug product. See, further down in this review, the evaluation of the applicant's response to Q 13b.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
Project Manager Name/Date

C. CC Block

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/s/

Eugenia Nashed
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CHEMIST

Ali Al-Hakim
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CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 1, 2008

TO: File N21-746

FROM: Eugenia Nashed, Ph.D.
CMC Reviewer, Division of Pre-marketing Assessment 1, ONDQA, CDER.

SUBJECT: Review Amendment (GMP Inspection)

NDA 21-746 Surfaxin (lucinactant) Intratracheal Suspension

This Memorandum provides an update to the CMC-related review activities since the filing of the Chemistry review on March 20, 2008.

A. The **Microbiology** Team finalized the NDA review on Apr 30, 2008, recommending an **APPROVABLE** action, with ten deficiencies to be addressed by the Applicant.

B. The Applicant has provided revised drug product labeling in amendment dated Apr 29, 2008. Upon review, the following comments concerning the **carton and vial labels** are proposed by the **CMC** team:

1. Submit revised mock up labels for all vial and carton presentations for the to-be-marketed drug product, including the following.

   a. Provide composition information.

   b. Specify dosage per kg of body weight.

   c. Include drug product volume per container, next to the drug product name.

   d. Emphasize the statements “Not for Injection” and “Single Use Vial”.

   e. Increase the prominence of the nonproprietary name “(lucinactant) Intratracheal Suspension”.

   f. Remove the promotional statement [redacted] (b) (4)

C. The final **EER** recommendation is **WITHHOLD** as of 4 pm on May 1, 2008.

The original EER for this NDA was submitted on May 11, 2004, and was re-submitted in this review cycle in November 2007. The EER was updated several times by this reviewer as new information became available from the Applicant. All prior inspections resulted in "Withhold Approval" recommendations from the Office of Compliance, i.e., Feb 2005, Oct 2005, Apr 2006 and Sep 2007. Based on the above, this reviewer requested a feed back from the inspection team. An excellent feed back and collaboration was provided by the GMP Investigator in the first two review cycles, however no information was provided in this review cycle.

The Applicant has provided NDA re-submission dated Oct 31, 2007, which was filed as a full response based on the applicant's statement that all manufacturing sites are ready for inspection. However, upon preliminary review and subsequent inquiry sent to Discovery Labs, it was determined that the drug product manufacturing site (Totowa, NJ) is closed for implementation of the manufacturing changes. In submission dated Dec. 7, 2007, the applicant stated that the site will be "operational and ready for inspection" on Feb 4, 2008. In submission dated Dec 20, 2007, the applicant informed that the Totowa site "will be operational and available for inspection on Feb 25, 2008. Based on the information in the EES system the manufacturing site was inspected in March 2008.

The CMC review team was contacted on Apr 28, 2008, by the Team Leader of DMPQ, Office of Compliance, CDER, regarding the Discovery manufacturing and testing site, in Princeton, NJ. The site was no longer listed in the Applicant's Dec 7, 2007 update to the NDA, and the Compliance team was asking to cancel the EER for the above site. This CMC reviewer requested on Apr 28, 2008, an update from the Applicant regarding the manufacturing and testing activities performed at the Princeton site, in support of this NDA. The applicant responded with submission dated Apr 29, 2008, requesting the withdrawal of the Princeton facility (ETN: 3004014223) from the application, stating that the site was not used in support of this NDA since July 31, 2006.

Since the site number provided by the applicant was different from the FEI number listed by EES Team (FEI: 3003976111) this reviewer has consulted the EES team asking whether this is the same facility. Ms. S. Ferguson advised that this is the same facility based on the Compliance database listing for Princeton, NJ. This reviewer canceled the EER for the Discovery facility in Princeton, NJ, on Apr 29, 2008. The final EER recommendation, Withhold, became available on May 1, 2008, at 4 pm. The withhold recommendation was based on the fact that the District was not able to conduct an inspection at one of the drug substance manufacturing sites (b) (4) by the user fee date. Other, 22 manufacturing and testing facilities listed in support of this NDA have AC status.

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/s/

Eugenia Nashed
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CHEMIST

SURFAXIN
(lucinactant)
Intratracheal Suspension,

NDA 21-746

Division Director Review - 2
From Chemistry, Manufacturing, and Controls

Applicant: Discovery Laboratories, Inc.
350 South Main St.
Doylestown, PA

Indication: Lung surfactant for prevention (b) (4) of respiratory distress syndrome (RDS) in premature infants, intended for intratracheal instillation.

Presentation: Sterile suspension of 8 mL (b) (4)
0.8 mg/mL sinapultide
22.5 mg/mL dipalmitoylphosphatidylcholine (DPPC)
7.5 mg/mL palmitoyloleoylphosphatidylglycerol (POPG)
4.05 mg/mL palmitic acid (PA)
in 10 mL Stoppered Glass Vial.

EER Status: **Pending**

Consults:

PharmTox	**Inadequate** – qualification of impurities -11-MAR-2008
PharmTox	**Inadequate** - bioassay animal model – 11-MAR-2008
DMETS	**Inadequate** 1-MAR-2006
Microbiology	**Pending**

EA – exclusion requested – granted in CMC review #1

Original Submission: 13-APR-2004

Resubmission: 1-NOV-2007

Drug Substance

There are four active ingredients: 21-amino acid peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

1. Sinapultide
L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine.
Molecular formula: $C_{126}H_{239}N_{26}O_{22}$; Molecular weight: 2470 Daltons.
Manufactured by: (b) (4)
DMF (b) (4) – Adequate

2. DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)
Molecular formula: $C_{40}H_{80}NO_8P$; Molecular weight: 734.05 Daltons.
Manufactured by: (b) (4)
DMF (b) (4) – Adequate

3. POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)
Molecular formula: $C_{40}H_{76}NPO_{10}Na$; Molecular weight: 771.00 Daltons.
Manufactured by: (b) (4)
DMF (b) (4) – Adequate

4. PA (palmitic acid; hexadecanoic acid)
Molecular formula: $C_{16}H_{32}O_2$; Molecular weight: 256.42 Daltons.
Manufactured by: (b) (4)
DMF (b) (4) – Adequate

Several deficiencies remain for the drug substances however and will be forwarded to the sponsor:

- The drug substance-related impurities for (b) (4) exceed the qualification threshold of 0.15% recommended by the ICH guidance Q3A. Reduce the acceptance criteria for impurities to NMT 0.15% or provide adequate safety data to qualify these impurities.

Conclusion
Drug substances are not satisfactory.

Drug Product

The drug product is manufactured by:

Discovery Labs (previously called Laureate Pharma)
Totowa, NJ

The drug product is a milky-white, buffered at pH 7.6, aqueous suspension containing the following ingredients per mL:

0.8 mg/mL sinapultide
22.5 mg/mL DPPC
7.5 mg/mL POPG

4.05 mg/mL PA
(b) (4)

The drug product is manufactured (b) (4) The drug product suspension (b) (4) nominal fill) is aseptically delivered into a sterile 10 mL glass vial (USP Type I (b) (4) glass) sealed with (b) (4) gray rubber stopper and red flip-off aluminum seal.

Final container drug product is intended for storage at 5°C ± 3°C.

Specifications for SURFAXIN (lucinactant) include: appearance; identification of four active ingredients; assay of four active ingredients; impurities (b) (4) (b) (4) pH; surface tension; *in vivo* activity; viscosity; sterility; bacterial endotoxins; particulates; and particle size.

The stability data, provided in the application, were collected on the drug product batches manufactured using an aseptic filling process that was not validated. The stability reports listed results gathered for an incomplete list of attributes. Notably, results for the impurity profiles and the biological activity were not reported. The applicant continues to collect stability data on three process validation batches.

Numerous deficiencies include:

- Drug product specifications for release and stability need to be revised to reflect PharmTox recommendations, manufacturing capability, and the data gathered.
- Manufacturing process was revised but the necessary CMC information was inadequate to be assessed.
- Stability protocols need to be revised based on the initial data presented for 9 and 12 months on three lots.
- Stability trends are noted that will preclude shelf life beyond 12 months based on the proposed PharmTox recommendations on acceptance criteria for impurities and bioassay.
- Impurity qualification study in ferrets supports the impurity specifications for the drug product except for impurity (b) (4) Therefore, the acceptance criterion for this impurity needs to be reduced to NMT (b) (4) or adequate safety data to qualify the proposed level need to be provided.
- Lucinactant bioassay in rabbits is not appropriately validated and several comments have been provided by the PharmTox reviewer.

Conclusion
Drug product is not acceptable

Additional Items:

The drug product manufacturing site, Laureate Pharma, Totowa, NJ, was purchased by the applicant on 30 Dec 2005. The applicant has withdrawn the deficiencies but has not addressed the deficiencies as per the Microbiology reviewer.

Labeling (preliminary package insert) was reviewed in this cycle. Labeling comments are being addressed by the review team.

Methods validation package, describing the test methods and validation procedures, including information supporting the reference standard, will be reviewed upon acceptable response to deficiencies.

Overall Conclusion
From a CMC perspective, the application is recommended to be **Approvable**.

Blair A. Fraser, Ph.D.
Director
DPA I/ ONDQA

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/s/

Blair Fraser
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CHEMIST

NDA 21-746

Surfaxin (lucinactant) Intratracheal Suspension

Discovery Laboratories, Inc.

Eugenia Nashed
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA 21-746

2. REVIEW #: 3

3. REVIEW DATE: 19-March-2008

4. REVIEWER: Eugenia Nashed

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	CDER Date	Assigned Date
Original NDA	13-Apr-2004	15-Apr-2004	26-Apr-2004
Amendment	29-Jun-2004	30-Jun-2004	12-Jul-2004
Amendment	13-Sep-2004	14-Sep-2004	16-Sep-2004
Amendment	19-Oct-2004	20-Oct-2004	25-Oct-2004
Amendment	15-Nov-2004	16-Nov-2004	24-Nov-2004
Amendment	23-Nov-2004	26-Nov-2004	13-Dec-2004
Amendment	04-Jan-2005	05-Jan-2005	10-Jan-2005
Amendment	06-Jan-2005	10-Jan-2005	18-Jan-2005
Amendment AZ	05-Oct-2005	11-Oct-2005	19-Oct-2005
Amendment BC	20-Jan-2006	24-Jan-2006	25-Jan-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	CDER Date	Assigned Date
Amendment AZ	31-Oct-2007	01-Nov-2007	19-Nov-2007
Amendment BC	05-Dec-2007	06-Dec-2007	17-Dec-2007
Amendment BC	07-Dec-2007	10-Dec-2007	23-Dec-2007
Amendment BC	20-Dec-2007	20-Dec-2007	10-Jan-2008
Amendment BC	21-Dec-2007	26-Dec-2007	10-Jan-2008
Amendment BC	18-Jan-2008	23-Jan-2008	11-Feb-2008
Amendment BC	29-Feb-2008	29-Feb-2008	13-Mar-2008

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Discovery Laboratories, Inc.

Address: 350 South Main Street, Suite 307, Doylestown, PA 18901

Representative: Christopher Schaber, PhD, Exec. V.P. Drug Dev. & Reg. Compl.

Telephone: (215) 340-4699 ext. 130

1. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Surfaxin

b) Non-Proprietary Name (USAN): Lucinactant Intratracheal Suspension

c) Code Name/# (ONDC only): KL_4

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

2. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Lung surfactant for premature infants

11. DOSAGE FORM: Intratracheal Suspension, 5.8 mL/kg body weight

12. STRENGTH/POTENCY: 0.86 mg/mL sinapultide, 22.5 mg/mL DPPC, 7.5 mg/mL POPG and 4.05 mg/mL PA.

13. ROUTE OF ADMINISTRATION: Intratracheal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

Chemistry Review Data Sheet

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

There are four active pharmaceutical ingredients (APIs) in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

- **Sinapultide**

L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine.

CAS 138531-07-4
Molecular formula: $C_{126}H_{239}N_{26}O_{22}$
Molecular weight: 2470

- **DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)**

CAS 63-89-8
Molecular formula: $C_{40}H_{80}NO_8P$
Molecular weight: 734.05

- **POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)**

CAS 13879-80-6
Molecular formula: $C_{40}H_{76}NPO_{10}Na$
Molecular weight: 771.00

- **PA (palmitic acid; hexadecanoic acid)**

CAS 57-10-3
Molecular formula: $C_{16}H_{32}O_2$
Molecular weight: 256.42

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]

(b) (4)	II	(b) (4)	(b) (4)	1	ADEQUATE Inadequate Inadequate	Rev #3: 11/3/05 Suong T. Tran Rev #2: 10/7/04 Rev #1: 7/9/04	Originally, 23 deficiencies were forwarded to the holder. Second review listed 7 remaining deficiencies. Review #3 yielded an Adequate status.
	II			1	ADEQUATE Inadequate Inadequate	 3/1/06 Eugenia Nashed 1/18/05 Edwin Jao	Written review by Art Shaw is pending Lack of adequate specifications for impurities and lack of stability data.
	II			1	ADEQUATE IR letter pending Inadequate	2/6/06 Art Shaw 1/19/05 Art Shaw	IR letter sent to the Holder 2/9/06. Inadequate impurity profile and stab. data.
(b) (4)	II	(b) (4)	(b) (4)	1	ADEQUATE IR letter pending Inadequate	2/9/06 Art Shaw 1/19/05 Art Shaw	IR letter sent to the Holder 2/9/06. Inadequate impurity profile and stab. data.
	II			1	Adequate Inadequate Inadequate	 3/2/06 Eugenia Nashed 1/14/05 Edwin Jao	DMF retired, sent request to holder to submit update to Jan 2000 amend. Lack of adequate specs for impurities and lack of stab. data
(b) (4)			(b) (4)	1	WITHDRAWN Inadequate Inadequate	 3/7/06 Vinayak Pawar 1/18/05 Vinayak Pawar	The applicant has purchased the manufacturing facility and became the new owner (1/06) of the DMF. DMF was withdrawn from the application on Oct 31, 2007. Two previous reviews of the DMF identified number of serious deficiencies.
(b) (4)				5	Not reviewed		Type I DMF for testing facility.

(b) (4)	III	(b) (4)	(b) (4)	1	ADEQUATE	3/23/04	
	III			1	ADEQUATE	10/21/99 Ravi Harapanhalli HFD-160	Also, adequate for similar formulation Rev 8/26/03 by J. Salemme, HFD-580.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 40,287 (b) (4)	Discovery Laboratories	Surfaxin Intratracheal Suspension	Active	N/A	IND drug product batches were manufactured at the (b) (4) site, which has "WITHHOLD" recommendation due to the multiple GMP violations (several inspections).

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EER	GMP compliance for DS and DP manufacturing and testing sites	Update resubmitted in Nov 2007 Update resubmitted in Nov 2005 5/11/04	PENDING Sep 2007: Withhold Approval Apr 2006: Withhold Approval Oct 2005: Withhold Approval Feb 2005: Withhold Approval	The GMP inspection in the drug product manufacturing site at Totowa, NJ, is pending. For 4 months most of this review cycle the site was not available for inspection due to the implementation of manufacturing and equipment changes, in response to the deficiency comments. All prior inspections identified serious GMP deficiencies and resulted in FDA Forms 483.

Chemistry Review Data Sheet

Pharm/Tox	Appropriateness of the method testing biological activity of the drug product in premature rabbits. Qualification of impurities in drug substance and drug product.	10/19/04 11/15/05	INADEQUATE 3/11/08, Huiqing Hao Inadequate 2/14/06, Huiqing Hao Inadequate 12/01/04, Huiqing Hao INADEQUATE 3/11/08, Huiqing Hao Inadequate 3/3/06, Huiqing Hao	PharmTox comments to be forwarded to the applicant PharmTox comments to be forwarded to the applicant
Biopharm	N/A			
Methods Validation	To be sent			Will be submitted upon review of applicant's response to the deficiencies
Division Of Medical Errors and Technical Support	Assessment of the proposed proprietary name	7/16/04	PENDING Inadequate Denise Toyer 3/1/06 Inadequate Denise Toyer 11/8/04	Name acceptable from promotional perspective. NOT RECOMMENDED due to sound-like and look-like similarities with other drug names. The name Surfaxin is NOT RECOMMENDED + labeling comments concerning safety
DDMAC	Adequacy of PI	7/16/04	PENDING Inadequate Jialynn Wang 10/18/04	Label needs multiple revisions
EA	Exclusion requested	N/A	Acceptable	See CMC review #1
Microbiology	Sterile manufacture, fill and testing of the drug product.	5/10/04	PENDING Inadequate 3/7/06, V. Pawar Inadequate 1/18/05, V. Pawar	Response to the prior deficiencies is under review by the Microbiology Team. The process validation data supporting the recent manufacturing changes have not been submitted for review, as of Mar 19, 2008.

The Chemistry Review for NDA 21-746

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC Team recommends APPROVABLE action for this NDA, pending satisfactory response to Microbiology deficiencies (lack of process validation data, review by Microbiology Team is pending), acceptable recommendation from the Office of Compliance and satisfactory resolution of the remaining CMC deficiencies, as outlined at the end of this review.

After three review cycles, a substantial number of serious deficiencies remains to be addressed by the applicant. The major deficiencies include a lack of sterility assurance during drug product manufacture (Microbiology and GMP), deficient method and acceptance criteria for biological activity of the drug product (PharmTox), inadequate qualifications of drug substance and drug product impurities (PharmTox) and deficient CMC controls and stability issues, as outlined at the end of this review. The GMP inspection is currently pending at the drug product manufacturing site (Totowa, NJ). The site failed four prior GMP inspections and was not available for inspection until Feb 25, 2008 (most of the current review cycle). For that reason the final outcome can not be captured in this review.

This drug product has an orphan drug designation since 10/18/95; AN 95-913. Originally, the Applicant requested a Priority NDA Review which was denied by the DPADP based on the fact that the data presented in the application do not convincingly demonstrate an improvement over the other marketed surfactant products.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product consists of an aqueous suspension (b) (4) of a synthetic, 21-aa peptide (sinapultide), dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG) and palmitic acid (PA). The amino acid sequence of

the sinapultide was designed to simulate the nature of the structure of the lung surfactant protein B (SP-B). [redacted] and to mimic the behavior of the *in vivo* system responsible for lowering surface tension in the lungs.

There are four active ingredients in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA). Each API is supported by the corresponding DMF - see the "Supporting DMFs" table above.

The drug product suspension is sterile-filled to 10 mL sterile glass vials and contains 0.862 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG and 4.05 mg/mL of PA, total 8 mL per vial. This corresponds to a concentration of 0.862 mg of peptide and 30 mg of total phospholipids per 1 mL of drug product suspension.

B. Description of How the Drug Product is Intended to be Used

Surfaxin (lucinactant) Intratracheal Suspension is intended for the prevention [redacted] of respiratory distress syndrome (RDS) in premature infants. It is a milky-white suspension intended for an intratracheal instillation to the lungs of premature neonates in a hospital setting. The proposed dose for Surfaxin is 5.8 mL/kg body weight/dose (5.0 mg of peptide and 174 mg phospholipids/kg body weight) for up to four doses in 24 h. The nominal fill is [redacted] of suspension per 10 mL sterile vial to be stored at 5°C ± 3 °C (refrigerator).

C. Basis for Approvability or Not-Approval Recommendation

This application is considered APPROVABLE from the CMC perspective pending satisfactory resolution of the remaining Microbiology, GMP, PharmTox and CMC issues. The major deficiencies include a lack of sterility assurance during drug product manufacture (Microbiology and GMP), deficient method and acceptance criteria for biological activity of the drug product (PharmTox), inadequate qualifications of drug substance and drug product impurities (PharmTox) and deficient CMC controls and stability issues, as outlined at the end of this review.

This is the third review cycle for this NDA and covers applicant's submissions dated Oct 31, 2007 (full response to Mar 31, 2006, letter), Dec 5, 2007 (Response to 483, dated Sep 24, 2007), Dec 7, 2007 (Response to Nov 29, 2007, CMC letter), Dec 20, 2007 (Response to Dec 11, 2007, CMC letter), Dec 21, 2007 (9 month stability data supporting the Oct 31, 2007, full response), Jan 18, 2008 (Response to Jan 11, 2008, CMC letter), Feb 29, 2008 (12 month stability data supporting the Oct 31, 2007, full response).

During two prior review cycles numerous serious deficiencies were identified, including inadequate characterization and release of APIs, inadequate drug product controls, inadequate impurity/decomposition profiles and lack of adequate supporting stability data. Also, multiple batch failures for sterility and/or biological activity at 6, 12 and 18 months of testing were observed.

Upon issuing second AE letter on Mar 31, 2006, the Division met with the applicant (Discovery Labs) on Dec 21, 2006, to discuss the serious deficiencies remaining and to chart a possible path forward for this application (see meeting minutes in DFS). Several drug product manufacturing process changes and change of the container closure stopper were implemented. Release and stability data for 3 drug product batches manufactured with the revised process at Totowa site in Jan/Feb 2007, were submitted – 12 month update on Feb 29, 2008. It is noted the newly manufactured drug product lots exhibit lesser variability of the release and stability data and the analytical methods have been improved. However, based on the submitted data and the currently proposed by the applicant acceptance criteria, the requested 12 month expiry period is barely supported. It should be noted that further revisions and tightening of the proposed acceptance criteria for biological activity is recommended by the PharmTox team.

From the CMC perspective the most serious issues pertain to the limited stability of the drug product (b) (4) (based on submitted Circular Dichroism data) and decreases the biological activity of the drug product. Additional update for pending stability data with a thorough statistical evaluation need to be submitted to evaluate applicant's proposal for the expiry date.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
Project Manager Name/Date

C. CC Block

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/s/

Eugenia Nashed
3/20/2008 06:13:58 AM
CHEMIST

Ali Al-Hakim
3/20/2008 09:51:18 AM
CHEMIST

SURFAXIN (lucinactant)
Intratracheal Suspension,

NDA 21-746

Summary of the Basis for the Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Discovery Laboratories, Inc.
350 South Main St.
Doylestown, PA

Indication: Lung surfactant for prevention (b) (4) of respiratory distress syndrome (RDS) in premature infants, intended for intratracheal instillation.

Presentation: Sterile suspension of 8 mL of (b) (4)
0.8 mg/mL sinapultide,
22.5 mg/mL dipalmitoylphosphatidylcholine (DPPC),
7.5 mg/mL palmitoyloleoylphosphatidylglycerol (POPG),
4.05 mg/mL palmitic acid (PA),
in 10 mL Stoppered Glass Vial.

EER Status: **Withhold Approval** 5-FEB-2006

Consults: OCPB – **Inadequate** – qualification of impurities - 3-MAR-2006
OCPB – **Inadequate** - bioassay animal model – 14-FEB-2006
DMETS – **Inadequate** 1-MAR-2006
EA – exclusion requested – granted in CMC review #1
Microbiology – **Inadequate** 7-MAR-2006

Original Submission: 13-APR-2004

Resubmission: 5-OCT-2005

Drug Substance

There are four active ingredients: 21-amino acid peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

1. Sinapultide
L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-Llysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine.

CAS 138531-07-4; Molecular formula: $C_{126}H_{239}N_{26}O_{22}$; Molecular weight: 2470 Daltons. Manufactured by: (b) (4) DMF (b) (4) Adequate.

2. DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)
CAS 63-89-8; Molecular formula: $C_{40}H_{80}NO_8P$; Molecular weight: 734.05 Daltons. Manufactured by: (b) (4) DMF (b) (4) and (b) (4) – **Inadequate**.

3. POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)
CAS 13879-80-6; Molecular formula: $C_{40}H_{76}NPO_{10}Na$; Molecular weight: 771.00 Daltons. Manufactured by: (b) (4) DMF (b) (4) Adequate.

4. PA (palmitic acid; hexadecanoic acid)
CAS 57-10-3; Molecular formula: $C_{16}H_{32}O_2$; Molecular weight: 256.42 Daltons. Manufactured by: (b) (4) DMF (b) (4) **Inadequate**.

APIs are supported by five DMFs. Currently, an Information Request has been sent to the DMF (b) (4) holder. Deficiency letters have been sent to holders of DMFs (b) (4) (b) (4)

Several deficiencies remain for the drug substances and include:

- Specifications for the active ingredients are inadequate.
- Impurity profiles need to be adequately resolved and individual impurities need to be identified. Unknown impurities reach (b) (4)
- Characterization, by the sponsor, of the active ingredients needs to be completed.

Conclusion
Drug substances are not satisfactory.

Drug Product

The drug product is manufactured by:

Laureate Pharma
Totowa, NJ

The drug product is a milky-white, buffered at pH 7.6, aqueous suspension containing the following ingredients per mL:

0.8 mg/mL sinapultide
22.5 mg/mL DPPC

7.5 mg/mL POPG
4.05 mg/mL PA
(b) (4)
Sodium Chloride USP (b) (4)

The drug product is manufactured by (b) (4) The drug product suspension (b) (4) nominal fill) is aseptically delivered into a sterile 10 mL glass vial (USP Type I (b) (4) glass) sealed with (b) (4) gray rubber stopper and red flip-off aluminum seal.

Final container drug product is intended for storage at 5°C ± 3°C.

Specifications for SURFAXIN (lucinactant) include: appearance; identification of four active ingredients; assay of four active ingredients; impurities (b) (4) (b) (4) pH; surface tension; *in vivo* activity; viscosity; sterility; bacterial endotoxins; particulates; and particle size.

The provided stability data were collected on the drug product batches manufactured under an aseptic filling process that was not validated. The provided results were collected for an incomplete list of attributes. Notably, results for the impurity profiles and the biological activity were missing from stability reports. The applicant continues to collect stability data on three process validation batches

Numerous deficiencies have been noted relating to:

- Sterility assurance during sterile-fill manufacture and storage - DMF (b) (4) is inadequate.
- (b) (4)
- Stability data for drug product – two batches failed sterility after 6 months; only one month data collected on complete attributes. (b) (4)
- Drug product specifications for release and stability testing are lacking.
- Lack of bridge between clinical and to-be-manufactured batches
- GMPs for drug product manufacture –Drug product manufacturing site failed GMP inspections.

Conclusion
Drug product is not acceptable

Additional Items:

The drug product manufacturing site ,Laureate Pharma, Totowa, NJ, was purchased by the applicant on 30 Dec 2005. The applicant committed (amendment dated 20-Jan-2006) to submit an update to the DMF that supports drug product manufacturing, sterile fill. DMF (b) (4) is **Inadequate**, dated 7-MAR-2006.

Labeling was not comprehensively reviewed in this cycle. The name Surfaxin is NOT RECOMMENDED. Additionally, the package insert and the label need multiple revisions.

Methods validation package, describing the test methods and validation procedures, including information supporting the reference standard, will be reviewed upon acceptable response to deficiencies.

Overall Conclusion
From a CMC perspective, the application is recommended for an approvable action.

Blair A. Fraser, Ph.D.
Chief
Branch II/DPA I/ ONDQA

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/s/

Blair Fraser
3/30/2006 07:41:18 AM
CHEMIST

Chi Wan Chen
3/30/2006 07:32:29 PM
CHEMIST

NDA 21-746

Surfaxin (lucinactant) Intratracheal Suspension

Discovery Laboratories, Inc.

Eugenia Nashed
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA 21-746

2. REVIEW #: 2

3. REVIEW DATE: 3-March-2006

4. REVIEWER: Eugenia Nashed

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	CDER Date	Assigned Date
Original NDA	13-Apr-2004	15-Apr-2004	26-Apr-2004
Amendment	29-Jun-2004	30-Jun-2004	12-Jul-2004
Amendment	13-Sep-2004	14-Sep-2004	16-Sep-2004
Amendment	19-Oct-2004	20-Oct-2004	25-Oct-2004
Amendment	15-Nov-2004	16-Nov-2004	24-Nov-2004
Amendment	23-Nov-2004	26-Nov-2004	13-Dec-2004
Amendment	04-Jan-2005	05-Jan-2005	10-Jan-2005
Amendment	06-Jan-2005	10-Jan-2005	18-Jan-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	CDER Date	Assigned Date
Amendment AZ	05-Oct-2005	11-Oct-2005	19-Oct-2005
Amendment BC	20-Jan-2006	24-Jan-2006	25-Jan-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Discovery Laboratories, Inc.

Address: 350 South Main Street, Suite 307, Doylestown, PA 18901

Chemistry Review Data Sheet

Representative: Christopher Schaber, PhD, Exec. V.P. Drug Dev. & Reg. Compl.

Telephone: (215) 340-4699 ext. 130

1. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Surfaxin

b) Non-Proprietary Name (USAN): Lucinactant Intratracheal Suspension

c) Code Name/# (ONDC only): KL_4

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

2. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Lung surfactant for premature infants

11. DOSAGE FORM: Intratracheal Suspension, 5.8 mL/kg body weight

12. STRENGTH/POTENCY: 0.8 mg/mL sinapultide, 22.5 mg/mL DPPC, 7.5 mg/mL POPG and 4.05 mg/mL PA.

13. ROUTE OF ADMINISTRATION: Intratracheal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

There are four active pharmaceutical ingredients (APIs) in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

- **Sinapultide**

L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine.

CAS 138531-07-4
Molecular formula: $C_{126}H_{239}N_{26}O_{22}$
Molecular weight: 2470

- **DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)**

CAS 63-89-8
Molecular formula: $C_{40}H_{80}NO_8P$
Molecular weight: 734.05

- **POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)**

CAS 13879-80-6
Molecular formula: $C_{40}H_{76}NPO_{10}Na$
Molecular weight: 771.00

- **PA (palmitic acid; hexadecanoic acid)**

CAS 57-10-3
Molecular formula: $C_{16}H_{32}O_2$
Molecular weight: 256.42

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate Inadequate ADEQUATE	Rev #1: 7/9/04 Rev #2: 10/7/04 Rev #3: 11/3/05 Suong T. Tran	Originally, 23 deficiencies were forwarded to the holder. Second review listed 7 remaining deficiencies. Review #3 yielded an Adequate status.

Chemistry Review Data Sheet

(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate INADEQUATE	1/18/05 Edwin Jao 3/1/06 Eugenia Nashed	Lack of adequate specifications for impurities and lack of stability data.
	II			1	Inadequate ADEQUATE IR letter pending	1/19/05 Art Shaw 2/6/06 Art Shaw	Inadequate impurity profile and stab. data. IR letter sent to the Holder 2/9/06.
	II			1	Inadequate ADEQUATE IR letter pending	1/19/05 Art Shaw 2//06 Art Shaw	Inadequate impurity profile and stab. data. IR letter sent to the Holder 2/9/06.
	II			1	Inadequate INADEQUATE	1/14/05 Edwin Jao 3/2/06 Eugenia Nashed	DMF retired, sent request to holder to submit update to Jan 2000 amend. Lack of adequate specs for impurities and lack of stab. data
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate INADEQUATE	1/18/05 Vinayak Pawar 3/7/06 Vinayak Pawar	Dec 13 '04 amendment for assurance of sterility during drug product manufacture was reviewed by Micro Team and found inadequate. Amendment dated 6/05 also inadequate. Ownership of DMF has changed (1/06) and an update will be submitted in Mar 2006.
	I			5	Not reviewed		Type I DMF for testing facility.
(b) (4)	III	(b) (4)	(b) (4)	1	ADEQUATE	3/23/04	The last amendment to the DMF dated 26-Aug-04 was not reviewed due to inability to obtain it from the CDR, despite multiple e-mail requests. Amendment will be reviewed in the second cycle.
	III			1	ADEQUATE	10/21/99 Ravi Harapanhalli HFD-160	Also, adequate for similar formulation Rev 8/26/03 by J. Salemme, HFD-580.

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 40,287 (b) (4)	Discovery Laboratories	Surfaxin Intratracheal Suspension	Active	N/A	IND drug product batches were manufactured at (b) (4) site, which has "WITHHOLD" recommendation due to the multiple GMP violations (several inspections).

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EER	GMP compliance for DS and DP manufacturing and testing sites (10 sites total) Additional site for peptide testing added (b) (4)	5/11/04 Update resubmitted in Nov 2005	Recommendation dated Feb 5, 2006, from the OC : WITHHOLD APPROVAL. This is based on the inadequate status of the drug product manufacturing site	The drug product manufacturing site in Totowa, NJ was inspected on Jan 5-11, 2005 and received Form 483 with multiple GMP deficiencies. In May 2004 the site was not ready for inspection - see note dated 6/10/04 in the EES by Ms. S. Ferguson.. Several other sites (Discovery Labs, drug product testing) have received also Form 483 with multiple comments regarding lack of SOPs, lack of validated methods and no follow-up on the out-of-specifications results. Currently, only drug product manufacturing site Totowa, NJ has inadequate status.
Pharm/Tox	Appropriateness of the method testing biological activity of the drug product in premature rabbits. Qualification of impurities in drug substance and drug product.	10/19/04 11/15/05	Inadequate 12/01/04, Huiqing Hao INADEQUATE 2/14/06, Huiqing Hao INADEQUATE 3/3/06, Huiqing Hao	6 comments to be forwarded to the applicant 3 comments to be forwarded to the applicant PharmTox omments to be forwarded to the applicant

Chemistry Review Data Sheet

Biopharm	N/A			
Methods Validation	To be sent			Will be submitted upon review of applicant's response to the deficiencies
Division Of Medical Errors and Technical Support	Assessment of the proposed proprietary name	7/16/04	Inadequate Denise Toyer 11/8/04 INADEQUATE Denise Toyer 3/1/06	Name acceptable from promotional perspective. NOT RECOMMENDED due to sound-like and look-like similarities with other drug names. The name Surfaxin is NOT RECOMMENDED + labeling comments concerning safety
DDMAC	Adequacy of PI	7/16/04	Inadequate Jialynn Wang 10/18/04	Label needs multiple revisions Second cycle review by DDMAC was not available during conclusion of the current CMC review
EA	Exclusion requested	N/A	Acceptable	See CMC review #1
Microbiology	Sterile manufacture, fill and testing of the drug product.	5/10/04	Inadequate 1/18/05, V. Pawar INADEQUATE 3/7/06, V. Pawar	Submitted microbiology data (only in Dec '04 to DMF (b) (4) are inadequate to support assurance of a sterile drug product manufacture. The NDA Applicant has bought the drug product manufacturing site (12/30/05) and is planning to submit an update to the DMF (b) (4) in Mar 2006.

The Chemistry Review for NDA 21-562

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC Team DOES NOT RECOMMEND APPROVAL for this NDA, based on the feedback from the Microbiology Team, a WITHHOLD APPROVAL recommendation from the Office of Compliance and multiple CMC deficiencies as outlined at the end of this review. The major deficiencies include a lack of sterility assurance during drug product manufacture (current manufacturing site failed the GMP inspection twice, and the previous site failed several GMP inspections), and unacceptable impurity/decomposition profile compounded by the lack of adequate stability data.

This drug product has an orphan drug designation since 10/18/95; AN 95-913. Originally, the Applicant requested a Priority NDA Review which was denied by the DPADP based on the fact that the data presented in the application do not convincingly demonstrate an improvement over the other marketed surfactant products. In addition, the applicant did not submit, in the original application, adequate clinical update and adequate stability data (only 3 months of incomplete data submitted) to accommodate the review timetable for a priority review.

After the 2 review cycles, a substantial number of serious CMC deficiencies remains to be addressed by the applicant. The conclusion from the NDA wrap-up meeting was to invite the applicant, after issuing the action letter, to present their plans regarding development of their drug product and addressing the remaining deficiencies (see Comment #1 at the end of this review).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product consists of an aqueous suspension [redacted] (b) (4) of a synthetic, 21-aa peptide (sinapultide), dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG) and palmitic acid (PA). The amino acid sequence of the sinapultide was designed to simulate the nature of the structure of the lung

surfactant protein B (SP-B). [redacted] and to mimic the behavior of the *in vivo* system responsible for lowering surface tension in the lungs.

There are four active ingredients in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA). Each API is supported by the corresponding DMF - see the "Supporting DMFs" table above.

The drug product suspension is sterile-filled to 10 mL sterile glass vials and contains 0.8 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG and 4.05 mg/mL of PA, total [redacted] per vial. This corresponds to a concentration of 0.8 mg of peptide and 30 mg of total phospholipids per 1 mL of drug product suspension.

B. Description of How the Drug Product is Intended to be Used

Surfaxin (lucinactant) Intratracheal Suspension is intended for the prevention [redacted] of respiratory distress syndrome (RDS) in premature infants. It is a milky-white suspension intended for an intratracheal instillation to the lungs of premature neonates in a hospital setting. The proposed dose for Surfaxin is 5.8 mL/kg body weight/dose (4.6 mg of peptide and 174 mg phospholipids/kg body weight) for up to four doses in 24 h. The nominal fill is [redacted] of suspension per 10 mL sterile vial to be stored at 5°C ± 3 °C (refrigerator).

C. Basis for Approvability or Not-Approval Recommendation

This application is NOT RECOMMENDED FOR APPROVAL from the CMC perspective due to the lack of sterility assurance during the drug product manufacture and multiple substantial CMC deficiencies. This is a sterile-fill drug product intended for use in premature infants *via* direct intratracheal instillation to the lungs. The Microbiology Team noted serious microbiology deficiencies in the NDA application and in the supporting DMF [redacted], and pointed out contradictory results for the same batch of media fill, reported in the NDA and in the DMF (see reviews dated Jan 14, and Jan 18, 2005, by Vinayak Pawar). The overall recommendation dated Feb 5, 2006, from the OC is to WITHHOLD APPROVAL for this application due to the serious GMP deficiencies at drug product manufacturing site at Totowa, NJ - see comments further down in this review and a copy of the EER summary at the end of this review. The drug product manufacturing site at Totowa has been bought (12/30/05) by the NDA applicant, who has committed (amendment dated 01/20/06) to submit in Mar 2006, an update to DMF [redacted], which is supporting drug product manufacture.

Also, numerous CMC deficiencies were noted regarding multiple batch failures for sterility and biological activity after 12-18 months of storage at label conditions, inadequate characterization and release of APIs, inadequate drug product controls, inadequate impurity/decomposition profiles and lack of adequate supporting stability data. See the end of this review for a full list of deficiencies.

It should be noted that the initially submitted CMC data and the readiness of the drug product manufacturing site were not adequate to perform a meaningful CMC review and/or GMP inspection at the manufacturing site for this drug product. However, on the advice of the DNDC II Director, the application was reviewed as submitted (see 45-Day CMC Review dated May 28, 2004), and the initial CMC comments were forwarded to the applicant in the Filing Letter dated June 25, 2004. These included the following:

1. Potentially serious compliance problems at the drug product manufacturing site, Laureate Pharma at Totowa, NJ - the site was not ready for inspection based on the note in the EES dated 6/10/04, by S. Ferguson. It should be noted that the previously used drug product manufacturing site (b) (4) received multiple "withhold" recommendations, due to serious GMP violations.

2. Only 3 months of stability data were submitted, contrary to our recommendation during pre-NDA meeting on Jun 13, 2003. Provided data were incomplete, with some attributes containing only one data point and some using "conform" entries, instead of numerical values.

3. Very limited data for the biological activity testing of the drug product were submitted, contrary to our recommendation during pre-NDA meeting on Jun 13, 2003, and a description of the analytical method was not provided.

4. The impurity profile was not established as of the submission date, and the proposed acceptance criteria for impurities were excessively wide, e.g., (b) (4) for individual unknown impurities and (b) (4) for total unknown impurities. The applicant was referred to the ICH Q3A and Q3B guidance for recommendations regarding identification and qualification of impurities.

The Applicant responded with NDA amendments dated Oct 19, Nov 15, and Nov 23, 2004, and Jan 4, and Jan 6, 2005, which was very close to end of the first review cycle (Div Goal date: Jan 9, 2004). Also, a 15 volume amendment dated Dec 13, 2005 was submitted to the DMF (b) (4) supporting the drug product manufacture. Upon review of all responses received up to Jan 14, 2004, the outstanding major deficiencies (30 CMC comments) were forwarded to the applicant in AE letter dated Feb 11, 2005.

The Applicant has provided submission dated July 29, 2005, in response to our AE letter. Upon preliminary review, the applicant's response was considered inadequate

to activate the review clock, i.e., incomplete response due to the lack of crucial data. A NOT-COMPLETE-RESPONSE letter dated Aug 16, 2005, pointing out an incomplete response to at least 13 comments from the AE letter, was forwarded to the Applicant. The Applicant has responded with submission dated Oct 5, 2005, and subsequent amendment dated Jan 20, 2006, informing about the change in ownership of the drug product manufacturing site. Upon review of all submissions received up to Mar 3, 2006, the outstanding major deficiencies include the following.

- **Deficient Sterile-Fill Process/Controls for Drug Product Manufacture.**

Applicant failed to submit data and information demonstrating assurance of sterile manufacture for this high-risk profile drug product. The (b) (4) manufacturing site (where the clinical batches were manufactured) has repeatedly failed the GMP inspection. The process was transferred to Laureate Pharma site that could not demonstrate successful media fill validation despite running over 9 media fill batches from (b) (4) The Microbiology Team noted serious deficiencies in the manufacturing process (see Micro review dated 3/3/06), and the Office of Compliance recommends a WITHHOLD APPROVAL for the drug product manufacturing site at Totowa, NJ. The site was owned and operated by Laureate Pharma. A conflicting data sets for the same batches were submitted by the drug product manufacturer (Failed) and by the NDA holder (Pass). On Dec 30, 2005 the site was purchased by the Discovery Labs at Doylestown, PA, who is the applicant for this NDA. The overall recommendation dated Feb 5, 2006, from the OC is to WITHHOLD APPROVAL for this application.

- **Inadequate Status of Drug Substance Supporting DMFs.**

Originally, all five DMFs supporting manufacturing and controls for the sinapultide, DPPC, POPG and PA had inadequate status. Currently, the DMF supporting sinapultide has an adequate status, after 3 review cycles. The DMFs supporting POPG (b) (4) have adequate status, with outstanding IR letters, after 2 review cycles. The DMFs (b) (4) supporting the manufacture and testing of DPPC and PA remain INADEQUATE after 2 review cycles, due to the deficient impurity profiles and lack of supportive stability data.

- **Inadequate status of DMF (b) (4) supporting drug product manufacture.**

The DMF was found inadequate upon initial review and additional data were requested from the holder. Upon multiple requests, a major amendment dated Dec 13, 2004, was submitted to this DMF. The supporting data for the sterile-fill in-process controls for the drug product manufacture were found INADEQUATE by the Microbiology Team. In addition, the submitted validation data (media fill) are contradictory (clearly positive findings) to the data submitted for the same media fill batch in the NDA (negative findings). Refer to the review by Vinayak Pawar dated Jan 18, 2005. DMF update dated Jun 2005 (partial response) was reviewed and found INADEQUATE to support the sterile-fill manufacture. The DMF's ownership has changed in Jan 2006, after Discovery has purchased the drug product

manufacturing site at Totowa, NJ. The new holder has committed to submit an update to the DMF in Mar 2006.

- **Deficient method and lack of adequate data for biological activity of the drug product.**

The original NDA application was submitted without a validated method and without numerical results for testing the biological activity of drug product. This was in a clear contradiction to our recommendation at the p-NDA meeting on Jun 25, 2003.

In response to our comments in the Filling letter (6/25/04), the Applicant has submitted a description of the analytical method dated Oct 19, 2004, with preliminary results for 2 data points for 2 stability batches. The principal design of the method (*in vivo* testing on premature rabbits) were reviewed by the PharmTox team, and found inadequate after 2 review cycles – see reviews by Huiqing Hao dated 12/01/04, and 02/14/06. Majority of the submitted drug product stability data do not contain results for the biological activity testing: not tested, or reported as "conforms".

- **Inadequate data and specifications for drug substance and drug product impurity profiles.**

Applicant did not submit adequate impurity profiles for all four APIs, nor for the drug product, with a full list of identified and unidentified individual impurities. There is a pronounced problem with the mass balance for the drug product upon storage. The amounts of active ingredients decrease by up to 19 % whereas hardly any impurities are reported. The proposed impurity specifications (b) (4) for individual unknown, and (b) (4) for total unknown impurities are in a clear contradiction to the ICH Q3A and Q3B recommendations. In the second review cycle, the applicant reported about 25% loss of the sinapultide peptide on stability, due to formation (b) (4) The attempted qualification of impurities was evaluated by the PharmTox team and found INADEQUATE – see review by Huiqing Hao dated 3/3/06.

- **Inadequate stability data.**

The provided stability data were collected on the drug product batches manufactured with a sterile-fill process that apparently can not be validated (see comments on the sterile-fill process above). In addition, the provided results were collected for incomplete list of attributes, and some results were reported as "conform" instead of numerical values. Most importantly, the impurity profile and the drug product biological activity test are missing from the majority of the submitted data. Out of the recently submitted stability update, 2 NDA stability batches failed the currently proposed acceptance criteria as follow:

SURF-0034: failed sterility at 12 months and biological activity at 18 months
SURF-0035: failed biological activity test at 18 months

SURF-0035: failed the *p* value for biological activity test at 6 months storage at 5°C – the applicant provided the **re-test values** in the report tables, and explained that the failure was "most likely due to a faulty sample preparation".

The applicant is continuing stability studies on the "process validation" batches 5065202, 5075204, and 5085206A (manufactured at Laureate Pharma, Totowa, NJ, in 6/05 and 8/05, with presumably validated process) with a testing protocol that does include testing for biological activity and more clearly resolved impurity profile. However, currently submitted data include only zero point testing on two batches and 1 month of testing on the third batch.

(b) (4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
Project Manager Name/Date

C. CC Block

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/s/

Eugenia Nashed
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CHEMIST

Prasad Peri
3/10/2006 05:18:03 PM
CHEMIST
Signing for Dr. Blair Fraser, Branch Chief

NDA 21-746

SURFAXIN (LUCINACTANT) Intratracheal Suspension,

CHEMISTRY DIVISION DIRECTOR REVIEW #1

Applicant:

Discovery Laboratories, Inc.
350 South Main St.
Doylestown, PA

Indication: Lung surfactant for neonatal respiritory distress syndrome

Presentation: 0.8 mg/mL sinapultide
22.5 mg/mL DPPC
7.5 mg/mL POPG
4.05 mg/mL PA
total volume (b) (4) in 10 mL stoppered vials

EER Status: Withold 10-FEB-2005

Consults: DMETS – Tradename: Surfaxin – not acceptable 8-NOV-2004
Statistics – None
EA – no consult - waiver requested – granted
Micro – comments to sponsor recommended - 19-JAN-2005
OCPB – consult on bioassay animal model – 1-NOV-2004

Post Approval Agreements or Commitments: None

The original NDA was received 13-APR-2003

The **drug substances** are:

There are four active ingredients in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

Sinapultide
L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-Llysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine.
CAS 138531-07-4
Molecular formula: $C_{126}H_{239}N_{26}O_{22}$

Molecular weight: 2470

(b) (4)

DMF (b) (4) - inadequate

DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)
CAS 63-89-8
Molecular formula: $C_{40}H_{80}NO_8P$
Molecular weight: 734.05

(b) (4)

DMF (b) (4) - inadequate

POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)
CAS 13879-80-6
Molecular formula: $C_{40}H_{76}NPO_{10}Na$
Molecular weight: 771.00

(b) (4)

DMF (b) (4) - inadequate

PA (palmitic acid; hexadecanoic acid)
CAS 57-10-3
Molecular formula: $C_{16}H_{32}O_2$
Molecular weight: 256.42

(b) (4)

DMF (b) (4) - inadequate

Information requests have been sent to each DMF holder.

Specifications for the APIs are inadequate.
Conclusion
Drug substances are not satisfactory.

The **drug product**: 0.8 mg/mL sinapultide
22.5 mg/mL DPPC
7.5 mg/mL POPG
4.05 mg/mL PA
total volume (b) (4) in 10 mL stoppered vials.

Manufacturer:

Lauteate Pharma
Totowa, NJ

The formulation is a simple buffered aqueous solution.

Numerous deficiencies have been noted relating to:
Sterility assurance
Drug substance characterization, specifications including impurities controls
Stability data for drug product
Drug product specifications, stability data
GMPs for drug product manufacture

Labeling was not comprehensively reviewed in this cycle. The name 30 mg phospholipids and 0.8 mg sinapultide/mL does nor take into account the PA present. Comments relating to the name should be removed from the deficiency letter – further discussion of the name is needed.

The overall Compliance recommendation is withold 10-FEB-2005

DMFs for the actives are unacceptable – the others DMFs are acceptable .
Conclusion
Drug product is not acceptable

Overall Conclusion
From a CMC perspective the application is recommended for an approvable action.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
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CHEMIST

CHEMIST 45-Day NDA REVIEW

ONDC/DNDC II for Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-746	**TRADE NAME:**	Surfaxin
APPLICANT/SPONSOR:	Discovery Laboratories, Inc.	**USAN NAME:**	Lucinactant
CHEMIST:	Eugenia M. Nashed, Ph.D.		
TEAM LEADER:	Rik Lostritto, Ph.D.	**CATEGORY:**	Lung surfactant
DATE OF REVIEW:	May 28, 2004	**ROUTE:**	Intratracheal instillation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
April 13, 2004	April 13, 2004	NDA 21-746	Paper submission in CTD format

RELATED APPLICATIONS

Document Date	Application Type	Comments
	IND 40,287	p-NDA meeting on Jun 13, 2003

REVIEW SUMMARY: This is a preliminary (45-day) CMC review of NDA for Surfaxin (lucinactant) Intratracheal Suspension for "the prevention of respiratory distress syndrome (RDS) in premature infants". Drug product is composed of several lipids (DPPC, POPG and PA) and synthetic KL_4 (sinapultide) peptide which contains 21 lysine (K) and leucine (L) residues arranged to mimic the binding site of lung surfactant protein B (SP-B).

The drug product has an orphan drug designation since 10/18/95; AN 95-913. The Applicant requested a Priority Review of the application which was denied by the Division based on the fact that the data presented in the application do not convincingly demonstrate an improvement over the other marketed surfactant products. In addition, the applicant did not submit adequate stability data (only 3 months with 1 data point for biological activity submitted) to accommodate the review timetable for a priority review.

OUTSTANDING ISSUES: Possibly serious problem with the drug product manufacturing site Laureate Pharma at Totowa, NJ (Note dated 6/10/04 from HFD-322 in the EER that the registration for this site was cancelled). EER for all sites, except (b) (4) (b) (4) is pending.

Awaiting adequate stability data - only 3 months data (1 data point for biological activity) submitted in contrary to our advice during p-NDA meeting on 6/13/03.

Consult to the Micro team ((b) (4)) is pending.

Impurity profile not worked out adequately yet.

Reviews of type II DMFs (b) (4) (b) (4) are pending.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	X	**FILEABLE** (WITH COMMENTS TO APPLICANT)		**NOT FILEABLE**		
		APPROVAL		**APPROVABLE**		**NOT APPROVABLE**
OTHER ACTION:						

1. DRUG SUBSTANCE

Name	Manufacturer	DMF
Sinapultide (KL_4); 21 aa	(b) (4)	(b) (4)
Dipalmitoylphosphatidylcholine (DPPC)		
Palmitoyloleoylphosphatidylglycerol (POPG)		
Palmitic acid (PA)		

The reviews of the type II DMFs (as listed above) are pending.

2. DRUG PRODUCT

Drug product is composed of several lipids (DPPC, POPG and PA) and synthetic KL_4 (sinapultide) peptide which contains 21 lysine (K) and leucine (L) residues arranged to mimic the binding site of lung surfactant protein B (SP-B). These active ingredients are suspended in (b) (4) forming a white to off-white suspension which is packaged to an (b) (4) nominal fill in a 10 mL glass vial with a rubber stopper.

Drug product component	Amount of component per 1 mL	Amount of component per vial[1]
Sinapultide (KL_4); 21 aa	0.8 mg	(b) (4)
Dipalmitoylphosphatidylcholine (DPPC)	22.5 mg	
Palmitoyloleoylphosphatidylglycerol (POPG)	7.5 mg	
Palmitic acid (PA)	4.05 mg	
(b) (4)		

[1] The vial refers to the proposed commercial presentation, which has a nominal 10 mL capacity and a (b) (4)

[2] (b) (4)

[3] (b) (4) Sodium Chloride USP (b) (4) mg/mL) (b) (4) with Glacial Acetic Acid USP and/or Sodium (b) (4) It is also sometimes referred to as (b) (4) may be obtained commercially or prepared as part of drug product manufacture. The cited amount is added, along with some (b) (4) (b) (4)

The proposed dose for Surfaxin is 175 mg phospholipids/kg or 5.8 mL/kg/dose for up to four doses.

The following represent a full list of manufacturing and testing sites for drug product:

The drug product is manufactured and filled into vials by:

Laureate Pharma, LP
710 Union Boulevard
Totowa, New Jersey 07512
Establishment Registration No. 3004014226

The drug product is tested for sterility by:

(b) (4)

The drug product is tested for bacterial endotoxins by:

Laureate Pharma, LP
201 College Road East
Princeton, New Jersey 08540
Establishment Registration No. 3004014223

The drug product is tested for particulate matter by:

(b) (4)

The drug product is tested for *in vivo* activity by:

(b) (4)

The drug product is tested for all other quality criteria and released by:

Discovery Laboratories
350 Main Street
Suite 307
Doylestown, PA 18901
Labeler Code 68628

The EER was submitted on May 11, 2004. Several of the manufacturing and analytical sites were not in the system so the help was requested from the Compliance team (e-mail dated May 11, 2004 to EESQUESTIONS) to complete the request. The Compliance team added three of the four requested sites to the system on Jun 8, 2004 and is in the process of adding the fourth site, (b) (4) The evaluation for the submitted sites is pending. The Compliance team informed us that the registration for the drug product manufacturer (Laureate Pharma at Totowa, NJ) was cancelled - see note dated 06/10/04 in the EES by Ms. S. Ferguson. The Project

Manager confirmed with the applicant the address of the drug product manufacturing site (this is the only manufacturing site for this drug product) to avoid any misunderstanding. Technically, all sites submitted in the application should be ready for inspection, so the issue of the filing (or refuse to file, RFT) of this NDA was discussed with the ONDC 2 Division Director, Dr. Eric Duffy and Michael Folkendt. It was recommended to this reviewer that the application should be filed and the potential problems with the drug product manufacturing site should be addressed during the CMC review.

Drug Product Manufacturing

Drug Product is manufactured and filled (b) (4) The consult to Microbiology team was requested on May 10, 2004 (e-mail to PM).

Drug Product Specifications

Detailed impurity profile has not been worked out yet. The proposed acceptance criteria for individual and total unknown (b) (4) substances are NMT (b) (4) and NMT (b) (4) respectively. Similarly, the (b) (4) unknown individual and total impurities are proposed as NMT (b) (4) and NMT (b) (4) respectively. Also, the proposed acceptance criteria for the activity-related attributes and for the drug substance content on stability seem to excessively wide, e.g., sinapultide peptide: (b) (4).

Container Closure

Packaging component	Supplier	DMF Reference
Type I (b) (4) glass vial, 10 mL nominal capacity	(b) (4)	
See Vol. 1 Mod. 1, Section 1.2.7, Letters of Authorization, Pg. 1		
(b) (4) rubber stopper (b) (4)	(b) (4)	
See Vol. 1 Mod. 1, Section 1.2.7, Letters of Authorization, Pg. 1		
Aluminum, red flip-off seal, (b) (4)	(b) (4)	
See Vol. 1 Mod. 1, Section 1.2.7, Letters of Authorization, Pg. 1		

The review of DMFs # (b) (4) and (b) (4) is pending.

Stability Data

Only 3 months of stability data (5°C, 15°C and 25°C/60%RH) for 2 batches manufactured at Laureate Pharma (new site) were submitted. Testing for biological activity was performed at 3 month data point only (no testing at release) with 1 batch "conform" and 1 batch "does not conform" results.

Also, supportive data for 2 batches (21-24 months stored at 5°C, 13°C and 25°C/60%RH) manufactured at (b) (4) site (it was discontinued due to the persistent GMP problems) were submitted. These data do not include testing for drug product biological activity.

3. TIMELINE FOR REVIEW

An estimated timeline for completion of the review is as follows.

NDA 21-746 Review Timeline

Milestone	Estimated Date of Completion
Submission Stamp Date	April 13, 2004
60-Day Review	June 10, 2004
IR letter to Applicant	September 30, 2004
Complete Review	December 31, 2004
Division Goal Date	January 14, 2005
PDUFA Date	February 13, 2005

4. COMMENTS TO SPONSOR

1. We note a possibly serious compliance problem with the submitted drug product manufacturing site. Provide an updated list of drug substance and drug product manufacturing and testing facilities with corresponding CFN or FEI registration numbers which are accurate and complete. Submit a detailed description of duties and responsibilities for each site for the manufacturing and testing batches used in clinical trials, stability studies and to-be-marketed drug product. Include certificates of analysis for the batches supporting this NDA.

2. Your submitted stability data for the drug product are in clear distinction to our previous advice, e.g., p-NDA meeting on June 13, 2004. Submit updated stability results to include 6 month, 9 month and other available data points as soon as possible. Provide statistical evaluation of changes-with-time for all parameters with emphasis on the activity-related parameters and impurity profile. Tighten the proposed acceptance criteria so that it is reflective of the data.

3. The currently submitted data for biological activity of the drug product are very limited. Submit additional release and stability data for this parameter with actual test results rather than "conform" and "does not conform" format.

4. The proposed acceptance criteria for drug product impurities are wide, e.g., (b) (4) for individual unknown impurities and (b) (4) for total unknown impurities. Refer to our ICH Q3B guidance for recommendations regarding identification and qualification of impurities.

5. You did not apply uniform pagination throughout the application and did not provide Table of Contents with page references. This requires additional time to locate and review the pertinent information which impedes a timely review. Include consecutive page numbers and provide the customary Table of Contents with references to volumes and pages in your future submissions.

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/s/

Eugenia Nashed
6/15/04 04:45:30 PM
CHEMIST

Richard Lostritto
6/15/04 05:27:28 PM
CHEMIST

NDA 21-746

Surfaxin (lucinactant) Intratracheal Suspension

Discovery Laboratories, Inc.

Eugenia Nashed
Division of New Drug Chemistry II
Office of New Drug Chemistry

Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA 21-746

2. REVIEW #: 1

3. REVIEW DATE: 24-January-2003

4. REVIEWER: Eugenia Nashed

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	13-Apr-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	CDER Date	Assigned Date
Original NDA	13-Apr-2004	15-Apr-2004	26-Apr-2004
Amendment	29-Jun-2004	30-Jun-2004	12-Jul-2004
Amendment	13-Sep-2004	14-Sep-2004	16-Sep-2004
Amendment	19-Oct-2004	20-Oct-2004	25-Oct-2004
Amendment	15-Nov-2004	16-Nov-2004	24-Nov-2004
Amendment	23-Nov-2004	26-Nov-2004	13-Dec-2004
Amendment	04-Jan-2005	05-Jan-2005	10-Jan-2005
Amendment	06-Jan-2005	10-Jan-2005	18-Jan-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Discovery Laboratories, Inc.

Address: 350 South Main Street, Suite 307, Doylestown, PA 18901

Chemistry Review Data Sheet

Representative: Christopher Schaber, PhD, Exec. V.P. Drug Dev. & Reg. Compl.

Telephone: (215) 340-4699 ext. 130

1. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Surfaxin

b) Non-Proprietary Name (USAN): Lucinactant Intratracheal Suspension

c) Code Name/# (ONDC only): KL_4

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

2. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Lung surfactant for premature infants

11. DOSAGE FORM: Intratracheal Suspension, 5.8 mL/kg body weight

12. STRENGTH/POTENCY: 0.8 mg/mL sinapultide, 22.5 mg/mL DPPC, 7.5 mg/mL POPG and 4.05 mg/mL PA.

13. ROUTE OF ADMINISTRATION: Intratracheal

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

There are four active ingredients in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA).

- **Sinapultide**

L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysine.

CAS 138531-07-4
Molecular formula: $C_{126}H_{239}N_{26}O_{22}$
Molecular weight: 2470

- **DPPC (1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine)**

CAS 63-89-8
Molecular formula: $C_{40}H_{80}NO_8P$
Molecular weight: 734.05

- **POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol)**

CAS 13879-80-6
Molecular formula: $C_{40}H_{76}NPO_{10}Na$
Molecular weight: 771.00

- **PA (palmitic acid; hexadecanoic acid)**

CAS 57-10-3
Molecular formula: $C_{16}H_{32}O_2$
Molecular weight: 256.42

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate Inadequate	Rev #1: 7/9/04 Rev #2: 10/7/04 Suong T. Tran	Originally, 23 deficiencies were forwarded to the holder. Currently, 7 deficiency comments remain to be addressed by the holder.

Chemistry Review Data Sheet

(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	1/18/05 Edwin Jao	Lack of adequate specifications for impurities and lack of stability data.
	II			1	Inadequate	1/19/05 Art Shaw	Inadequate impurity profile and stability data.
	II			1	Inadequate	1/14/05 Edwin Jao	DMF retired, sent request to holder to submit update to Jan 2000 amend. Lack of adequate specs for impurities and lack of stability data
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	1/18/05 Vinayak Pawar	Dec 13 '04 amendment for assurance of sterility during drug product manufacture was reviewed by Micro Team and found inadequate.
	I			5	Not reviewed		Type I DMF for testing facility.
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	3/23/04	The last amendment to the DMF dated 26-Aug-04 was not reviewed due to inability to obtain it from the CDR, despite multiple e-mail requests. Amendment will be reviewed in the second cycle.
	III			1	Adequate	10/21/99 Ravi Harapanhalli HFD-160	Also, adequate for similar formulation Rev 8/26/03 by J. Salemme, HFD-580.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
IND 40,287 (b) (4)	Discovery Laboratories	Surfaxin Intratracheal Suspension	Active	N/A	IND drug product batches were manufactured at (b) (4) site, which has "WITHHOLD" recommendation due to the multiple GMP violations.

18. CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
EER	GMP compliance for DS and DP manufacturing and testing sites (9 sites total)	5/11/04	Final recommendation is not available from the OC yet. Based on the preliminary feedback from the GMP Investigators, the recommendation will be WITHHOLD APPROVAL for the drug product manufacturing and testing sites.	The drug product manufacturing site in Totowa, NJ was inspected on Jan 5-11, 2005 and received Form 483 with multiple GMP deficiencies. In May 2004 the site was not ready for inspection - see note dated 6/10/04 in the EES by Ms. S. Ferguson.. Several other sites (Discovery Labs, drug product testing) have received also Form 483 with multiple comments regarding lack of SOPs, lack of validated methods and no follow-up on the out-of-specifications results.
Pharm/Tox	Appropriateness of the method testing biological activity of the drug product in premature rabbits.	10/19/04	Inadequate 12/01/04 Huiqing Hao	6 comments to be forwarded to the applicant
Biopharm	N/A			
Methods Validation	To be sent			Will be submitted upon review of applicant's response to the deficiencies
Division Of Medical Errors and Technical Support	Assessment of the proposed proprietary name	7/16/04	Not recommended. Denise Toyer 11/8/04	Name acceptable from promotional perspective. NOT recommended due to sound-like and look-like similarities with other drug names.
DDMAC	Adequacy of PI	7/16/04	Label needs revision Jialynn Wang 10/18/04	
EA	Exclusion requested	N/A	Acceptable	
Microbiology	Sterile manufacture, fill and testing of the drug product.	5/10/04	Inadequate V. Pawar 1/18/04	Submitted microbiology data (only in Dec '04 to DMF (b) (4) are inadequate to support assurance of a sterile drug product manufacture.

The Chemistry Review for NDA 21-562

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC Team recommends NOT-APPROVAL for this NDA, based on the feedback from the Microbiology Team, a WITHHOLD APPROVAL recommendation from the Office of Compliance and multiple CMC deficiencies as outlined at the end of this review. The major deficiencies include a lack of sterility assurance during the drug product manufacture, and unacceptable impurity profile compounded by the lack of stability data.

The drug product has an orphan drug designation since 10/18/95; AN 95-913. The Applicant requested a Priority Review of the application which was denied by the DPADP based on the fact that the data presented in the application do not convincingly demonstrate an improvement over the other marketed surfactant products. In addition, the applicant did not submit, in the original application, adequate clinical update and adequate stability data (only 3 months of incomplete data submitted) to accommodate the review timetable for a priority review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product consists of an aqueous suspension (b) (4) of a synthetic, 21-aa peptide (sinapultide), dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG) and palmitic acid (PA). The amino acid sequence of the sinapultide was designed to simulate the nature of the structure of the lung surfactant protein B (SP-B). (b) (4) to mimic the behavior of the *in vivo* system responsible for lowering surface tension in the lungs.

There are four active ingredients in this drug product: 21-aa peptide (sinapultide), two phospholipids (DPPC and POPG), and palmitic acid (PA). Each drug substance is supported by the corresponding DMFs - see the "Supporting DMFs" table above.

The drug product suspension is sterile-filled to 10 mL sterile glass vials and contains 0.8 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG and 4.05 mg/mL of PA, total (b) (4) per vial. This corresponds to a concentration of 0.8 mg of peptide and 30 mg of total phospholipids per 1 mL of drug product suspension.

B. Description of How the Drug Product is Intended to be Used

Surfaxin (lucinactant) Intratracheal Suspension is indicated for "the prevention of respiratory distress syndrome (RDS) in premature infants". It is intended for an intratracheal instillation to the lungs of premature infants in the hospital. The proposed dose for Surfaxin is 5.8 mL/kg body weight/dose (4.6 mg of peptide and 174 mg phospholipids/kg body weight) for up to four doses in 24 h. The nominal fill is (b) (4) of suspension per 10 mL sterile vial to be stored at 5°C ± 3 °C (refrigerator).

C. Basis for Approvability or Not-Approval Recommendation

This application is RECOMMENDED TO BE NOT APPROVABLE from the CMC perspective due to the lack of sterility assurance during the drug product manufacture and multiple substantial CMC approvability issues. This is a sterile-fill drug product intended for use in premature infants *via* direct intratracheal instillation to the lungs. The Microbiology Team noted serious microbiology deficiencies in the NDA application and in the supporting DMF (b) (4), and pointed out contradictory results for the same batch of media fill, reported in the NDA and in the DMF (see reviews dated Jan 14, and Jan 18, 2005 by Vinayak Pawar). The final recommendation from the OC is not available yet at the time of this review, however the preliminary feedback from the Field Investigators indicate a WITHHOLD APPROVAL recommendation for this application due to the serious GMP deficiencies at drug product manufacturing and testing sites - see comments further down in this review and a copy of the EER summary at the end of this review.

Also, numerous CMC deficiencies were noted regarding characterization and release of drug substances, drug product controls, inadequate impurity profile and lack of supporting stability data. See the end of this review for a full list of deficiencies.

It should be noted that the initially submitted CMC data and the readiness of the drug product manufacturing site were not adequate to perform a meaningful CMC review and/or GMP inspection at the manufacturing site for this drug product. However, on the advice of the DNDC II Director, the application was reviewed as submitted (45-Day CMC Review dated May 28, 2004), and the initial CMC

comments were forwarded to the applicant in the Filing Letter dated June 25, 2004. These included the following:

1. Potentially serious compliance problems at the drug product manufacturing site, Laureate Pharma at Totowa, NJ - the site was not ready for inspection based on the note in the EES dated 6/10/04, by Ms. S. Ferguson. It should be noted that the previously used drug product manufacturing site (b) (4) received multiple "withhold" recommendations, based on a serious GMP violations.

2. Only 3 months of stability data were submitted, contrary to our recommendation during pre-NDA meeting on Jun 13, 2003. Provided data were incomplete, with some attributes containing only one data point and some using "conform" entries, instead of numerical values.

3. Very limited data for the biological activity testing of the drug product were submitted and a description of the analytical method was not provided.

4. The impurity profile was not clarified as of the submission date, and the proposed acceptance criteria for impurities were excessively wide, e.g., (b) (4) for individual unknown impurities and (b) (4) for total unknown impurities. The applicant was referred to the ICH Q3B guidance for recommendations regarding identification and qualification of impurities.

The Applicant responded with NDA amendments dated Oct 19, Nov 15, and Nov 23, 2004, and Jan 4, and Jan 6, 2005. Also, a 15 volume amendment dated Dec 13, 2005 was submitted to the DMF (b) (4) supporting the drug product manufacture. Upon review of all responses received up to Jan 14, 2004, the outstanding major deficiencies include the following.

- **Deficient Sterile-Fill Process/Controls for Drug Product Manufacture.**

Applicant failed to submit data and information demonstrating assurance of sterile manufacture for this high-risk profile drug product. The (b) (4) manufacturing site (where the clinical batches were manufactured) has repeatedly failed the cGMP inspection. The process was transferred to Laureate Pharma site that could not demonstrate successful media fill validation despite running over 9 media fill batches from (b) (4). The Microbiology Team noted serious deficiencies in the manufacturing process, and the GMP Investigators recommend a WITHHOLD APPROVAL for the drug product manufacturing and testing sites (Laureate Pharma at Totowa, NJ, and Discovery Labs at Doylestown, PA, who is the applicant for this NDA).

- **Inadequate status of all four supporting DMFs for drug substances.**

All DMFs supporting manufacturing and controls for the sinapultide, DPPC, POPG and PA have currently INADEQUATE status. The DMF for sinapultide was

reviewed Jul 7, 2004 (23 deficiencies) and the response to our letter was reviewed on Oct 7, 2004, with 7 deficiencies remaining. The DMFs (b) (4) supporting the manufacture and testing of DPPC, POPG and PA were found inadequate upon initial reviews, and DMF updates were requested from the holders. The responses dated Jan 4, 2005, Aug 24, 2004, and Jan 4, 2005, to each DMF respectively, were reviewed and found INADEQUATE due to the deficient impurity profiles and lack of supportive stability data.

- **Inadequate status of DMF (b) (4) supporting drug product manufacture.**

The DMF was found inadequate and additional data were requested from the holder. Upon multiple requests, a major amendment dated Dec 13, 2004 was submitted to this DMF. The supporting data for the sterile-fill in-process controls for the drug product manufacture were found INADEQUATE by the Microbiology Team. In addition, the submitted validation data (media fill) are contradictory (clearly positive findings) to the data submitted for the same media fill batch in the NDA (negative findings). Refer to the review by Vinayak Pawar dated Jan 18, 2005.

- **Lack of acceptable method and data for testing biological activity of the drug product.**

The original NDA application was submitted without a validated method and without numerical results for the biological activity of the drug product. This was in clear contradiction to our recommendation at the p-NDA meeting on Jun 25, 2003.
In response to the Filling letter, the Applicant has submitted a description of the analytical method dated Oct 19, 2004, with preliminary results for 2 data points for 2 stability batches. The principal design of the method (*in vivo* testing on premature rabbits) were reviewed by the PharmTox team, and found inadequate (Huiqing Hao 12/01/04) - see comments at the end of this review.

- **Inadequate data and specifications for drug substance and drug product impurity profiles.**

Applicant did not submit adequate impurity profiles any of the drug substances or for the drug product, with a full list of identified and unidentified individual impurities. There is a pronounced problem with the mass balance for the drug product upon storage. The amounts of active ingredients decrease by up to 19 % whereas hardly any impurities are reported. The proposed impurity specifications (b) (4) (b) (4) for individual unknown, and (b) (4) for total unknown impurities are in a clear contradiction to the ICH Q3A and Q3B recommendations.

- **Inadequate stability data.**

The provided stability data were collected on the drug product batches manufactured with a sterile-fill process that apparently can not be validated (see comments on the sterile-fill process above). In addition, the provided results were collected for incomplete list of attributes, and some results were reported as "conform" instead of numerical values. The submitted results on the temperature cycling studies (15-20 min at 44°C, 30 min at room temp and 24 h in refrigerator), photostability studies

and short term (24 h, 50 °C) stability studies do not include results for all relevant stability-related attributes. Most importantly, the impurity profile and the drug product biological activity test are missing from the majority of the submitted data.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
Project Manager Name/Date

C. CC Block

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/s/

Eugenia Nashed
1/25/05 02:26:43 PM
CHEMIST

Richard Lostritto
1/25/05 03:27:39 PM
CHEMIST

MEMORANDUM

DATE: November 3, 2003

TO: Dr. Craig Bertha

FROM: Chong-Ho Kim, Ph.D.

CC: Ms. Christine Yu
IND 40,287 file

SUBJECT: Comments on the Proposal for the Surfaxin drug product stability data to be included in the NDA at the time of filing.

Sponsor (Discovery Laboratories, Inc.) has identified and is in the process of establishing a second drug product manufacturing site: [redacted] (b) (4).

The sponsor is proposing a modification to the agency's recommendation from the June 13, 2003 meeting for drug product stability data submitted with the NDA (IC dated October 3, 2003). The proposal was reviewed and I have the following comments:

1. Your proposal of the stability data from [redacted] (b) (4) is acceptable.

2. a). As we indicated during the pre-NDA meeting on June 13, 2003, *at the time of NDA submission you need 6 months of stability data for at least 3 batches of the drug product manufactured at the new facility.* However, with the supportive stability data from [redacted] (b) (4) (proposal #1), you have to provide 6 months of stability data for at least 2 batches of the drug product manufactured at the new facility. (Two batches of 30 mg/mL and two batches of 10 mg/mL)

   b). During the NDA review period, you should provide at least three (3) additional months (nine months overall) of long-term primary stability data for two batches of 30 mg/mL and two batches of 10 mg/mL which were manufactured at [redacted] (b) (4).

CONCLUSION: The proposal is not acceptable. The above comments should be conveyed to the sponsor.

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/s/

Chong-Ho Kim
11/4/03 08:30:18 AM
CHEMIST

Craig Bertha
11/4/03 08:47:16 AM
CHEMIST
I concur.