

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021746Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2013 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <b>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</b>		NDA NUMBER NDA 21-746	
		NAME OF APPLICANT/NDA HOLDER Discovery Laboratories, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Surfaxin			
ACTIVE INGREDIENT(S) sinapultide, dipalmitoylphosphatidylcholine, palmitoyl-oleoyl phosphatidylglycerol, sodium salt and palmitic acid		STRENGTH(S) 30 mg/mL	
DOSAGE FORM suspension			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
<b>1. GENERAL</b>			
a. United States Patent Number 5,407,914		b. Issue Date of Patent 4/18/1995	
		c. Expiration Date of Patent 11/17/2011	
d. Name of Patent Owner The Scripps Research Institute		Address (of Patent Owner) 10550 North Torrey Pines Road	
		City/State La Jolla, CA	
		ZIP Code 92037	FAX Number (if available)
		Telephone Number 1 (858) 784-1000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?			
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			

FORM FDA 3542a (10/10)

Discovery Laboratories, Inc.  
 NDA 21-746  
 Module 1, Volume 1

Page 1

PSC Graphics (301) 423-1090 EF

Confidential  
 September 2011

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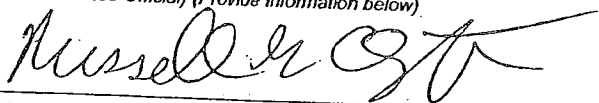
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.	
<b>2. Drug Substance (Active Ingredient)</b>	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
<b>3. Drug Product (Composition/Formulation)</b>	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
3.2 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
<b>4. Method of Use</b>	
Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
8, 9, 12	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS.
<b>5. No Relevant Patents</b>	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

## 6. Declaration/Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

9/2/2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Russell G. Clayton Sr., DO	
Address 2600 Kelly Road Suite 100	
City/State Warrington, PA	
ZIP Code 18976	Telephone Number (215) 488-9470
FAX Number (if available) (215) 488-9512	E-Mail Address (if available) rclayton@discoverylabs.com


The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

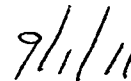
Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*



This application cites a published reference "Acute and sustained effects of lucinactant versus poractant alfa on pulmonary gas exchange and mechanics in premature lambs with respiratory distress syndrome. Gastiasoro-Cuesta E. et al. Pediatrics 117: 295-303, 2006." To the best knowledge and in the opinion of Discovery Laboratories, Inc., the study represented in this published reference is not related to any patents that claim the drug lucinactant or the use of such drug.

  
\_\_\_\_\_  
Russell G. Clayton Sr., DO  
Senior Vice President, Research and  
Development  
Discovery Laboratories, Inc.  
2600 Kelly Road  
Suite 100  
Warrington, PA 18976

  
\_\_\_\_\_  
Date

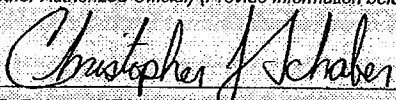
Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
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		NAME OF APPLICANT / NDA HOLDER Discovery Laboratories, Inc.	
<b>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</b>			
TRADE NAME (OR PROPOSED TRADE NAME) Surfaxin			
ACTIVE INGREDIENT(S) Sinapullide		STRENGTH(S) 30 mg/ml	
DOSAGE FORM Suspension			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
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<b>1. GENERAL</b>			
a. United States Patent Number 5,407,914		b. Issue Date of Patent 04/18/1995	
c. Expiration Date of Patent 11/10/2010			
d. Name of Patent Owner The Scripps Research Institute		Address (of Patent Owner) 10550 North Torrey Pines Road	
		City/State La Jolla, CA	
ZIP Code 92037		FAX Number (if available)	
Telephone Number (858) 784-1000		E-Mail Address (if available)	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
ZIP Code		FAX Number (if available)	
Telephone Number		E-Mail Address (if available)	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

FORM FDA 3542a (7/03)

Page 1

PSC Media Arts (301) 443-1090 EF

<b>For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.</b>		
<b>2. Drug Substance (Active Ingredient)</b>		
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).		<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		<input type="checkbox"/> Yes <input type="checkbox"/> No
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3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)		<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>4. Method of Use</b>		
<b>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</b>		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Claim Number (as listed in the patent) 8, 9, 12.	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	
<b>5. No Relevant Patents</b>		
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.		<input type="checkbox"/> Yes

<b>6. Declaration Certification</b>	
<b>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</b>	
<b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b>	
<b>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</b>	<b>Date Signed</b>
	3/5/04
<b>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</b>	
<b>Check applicable box and provide information below.</b>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<b>Name</b> Christopher J. Schaber, Ph.D.	
<b>Address</b> Discovery Laboratories, Inc. 350 South Main Street, Suite 307	<b>City/State</b> Doylestown, PA
<b>ZIP Code</b> 18901	<b>Telephone Number</b> (215) 340-4699
<b>FAX Number (if available)</b> (215) 340-3940	<b>E-Mail Address (if available)</b>
<p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

Department of Health and Human Services Food and Drug Administration  <b>PATENT INFORMATION SUBMITTED WITH THE          FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and          Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
		NDA NUMBER	
		21-746	
		NAME OF APPLICANT / NDA HOLDER	
		Discovery Laboratories, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME)			
Surfaxin			
ACTIVE INGREDIENT(S)		STRENGTH(S)	
SNapultide		30 mg/ml	
DOSAGE FORM			
Suspension			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.</p>			
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<p><b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b></p>			
<p><b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b></p>			
<b>1. GENERAL</b>			
a. United States Patent Number		b. Issue Date of Patent	c. Expiration Date of Patent
5,260,273		11/09/1993	11/18/2009
d. Name of Patent Owner		Address (of Patent Owner)	
The Scripps Research Institute		10550 North Torrey Pines Road	
		City/State	
		La Jolla, CA	
		ZIP Code	FAX Number (if available)
		92037	
		Telephone Number	E-Mail Address (if available)
		(858) 784-1000	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

FORM FDA 3542a (7/03)

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PSC Media Arts (201) 443-1090 EF

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2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
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2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
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2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
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<b>4. Method of Use</b>		
<b>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</b>		
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
2	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Treatment of Infant Respiratory Distress Syndrome	
<b>5. No Relevant Patents</b>		
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.		<input type="checkbox"/> Yes

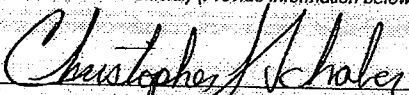
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Date Signed



3/5/04

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☒ NDA Applicant/Holder☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official☐ Patent Owner☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Christopher J. Schaber, Ph.D.

Address

Discovery Laboratories, Inc.  
350 South Main Street, Suite 307

City/State

Doylestown, PA

ZIP Code

18901

Telephone Number

(215) 340-4699

FAX Number (if available)

(215) 340-3940

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

Department of Health and Human Services Food and Drug Administration  <b>PATENT INFORMATION SUBMITTED WITH THE          FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and          Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
		NDA NUMBER 21-746	
		NAME OF APPLICANT / NDA HOLDER Discovery Laboratories, Inc.	
<b>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</b>			
TRADE NAME (OR PROPOSED TRADE NAME) Surfaxin			
ACTIVE INGREDIENT(S) Sinapultide		STRENGTH(S) 30 mg/ml	
DOSAGE FORM Suspension			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.</p>			
<p><b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.</p>			
<p><b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b></p>			
<p><b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b></p>			
<b>1. GENERAL</b>			
a. United States Patent Number 5,789,381		b. Issue Date of Patent 08/04/1998	c. Expiration Date of Patent 08/05/2015
d. Name of Patent Owner The Scripps Research Institute, Inc.		Address (of Patent Owner) 10550 North Torrey Pines Road	
		City/State La Jolla, CA	
		ZIP Code 92037	FAX Number (if available)
		Telephone Number (858) 784-1000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input type="checkbox"/> No

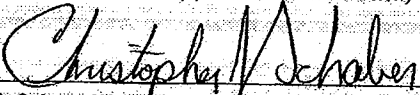
FORM FDA 3542a (7/03)

Page 1

PSC Media Arts (301) 443-1050 EF



<b>For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.</b>	
<b>2. Drug Substance (Active Ingredient)</b>	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
<b>3. Drug Product (Composition/Formulation)</b>	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
3.2 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
<b>4. Method of Use</b>	
<b>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</b>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Claim Number (as listed in the patent): 4, 5, 6.	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Treatment of Infant Respiratory Distress Syndrome.
<b>5. No Relevant Patents</b>	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

<b>6. Declaration Certification</b>	
<b>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</b>	
<b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b>	
<b>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</b>	<b>Date Signed</b>
	3/5/04
<b>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</b>	
<b>Check applicable box and provide information below.</b>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<b>Name</b> Christopher J. Schaber, Ph.D.	
<b>Address</b> Discovery Laboratories, Inc. 350 South Main Street, Suite 307	<b>City/State</b> Doylestown, PA
<b>ZIP Code</b> 18901	<b>Telephone Number</b> (215) 340-4699
<b>FAX Number (if available)</b> (215) 340-3940	<b>E-Mail Address (if available)</b>
<p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

Department of Health and Human Services Food and Drug Administration  <b>PATENT INFORMATION SUBMITTED WITH THE          FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and          Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
		NDA NUMBER	
		21-746	
		NAME OF APPLICANT / NDA HOLDER	
		Discovery Laboratories, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME)			
Surfaxin			
ACTIVE INGREDIENT(S)		STRENGTH(S)	
Sinapultide		30 mg/ml	
DOSAGE FORM			
Suspension			
<p>This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.</p>			
<p><b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.</p>			
<p><b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b></p>			
<p><b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b></p>			
<b>1. GENERAL</b>			
a. United States Patent Number		b. Issue Date of Patent	
5,952,303		09/14/1999	
		c. Expiration Date of Patent	
		03/30/2017	
d. Name of Patent Owner		Address (of Patent Owner)	
Ortho Pharmaceutical Corporation		1000 U.S. Route 202 South	
		City/State	
		Raritan, NJ	
		ZIP Code	FAX Number (if available)
		08869	
		Telephone Number	E-Mail Address (if available)
		(800) 682-6532	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

FORM FDA 3542a (7/03)

Page 1

FSC Media Arts (301) 443-1099 EF

<b>For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.</b>	
<b>2. Drug Substance (Active Ingredient)</b>	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.6 Does the patent claim only an intermediate?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
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<b>3. Drug Product (Composition/Formulation)</b>	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
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3.2 Does the patent claim only an intermediate?	
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3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
<b>4. Method of Use</b>	
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<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
<b>5. No Relevant Patents</b>	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed

*Christopher J. Schaber*

3/5/04

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

☒ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Christopher J. Schaber, Ph.D.

Address

Discovery Laboratories, Inc.  
350 South Main Street, Suite 307

City/State

Doylestown, PA

ZIP Code

18901

Telephone Number

(215) 340-4699

FAX Number (if available)

(215) 340-3940

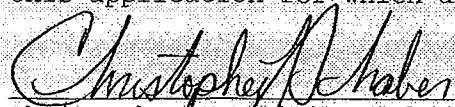
E-Mail Address (if available)

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Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

The undersigned declares that Patent No. 5,260,273, covers the formulation, composition, and/or method of use of Surfaxin® (lucinactant). This product is the subject of this application for which approval is being sought.



Christopher J. Schaber, Ph.D.  
Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

3/16/04  
Date

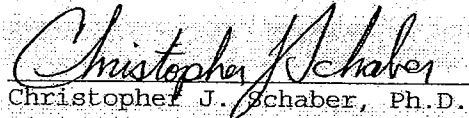
The undersigned declares that Patent No. 5,407,914, covers the formulation, composition, and/or method of use of Surfaxin® (lucinactant). This product is the subject of this application for which approval is being sought.



Christopher J. Schaber, Ph.D.  
Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

3/16/04  
Date

The undersigned declares that Patent No. 5,789,381, covers the formulation, composition, and/or method of use of Surfaxin® (lucinactant). This product is the subject of this application for which approval is being sought.

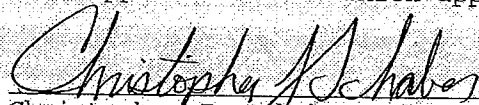
  
Christopher J. Schaber, Ph.D.

Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

3/16/04  
Date



The undersigned declares that Patent No. 5,952,303, covers the formulation, composition, and/or method of use of Surfaxin® (lucinactant). This product is the subject of this application for which approval is being sought.



Christopher J. Schaber, Ph.D.  
Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

3/16/04  
Date

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 21-746 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: 570/DPARP PDUFA Goal Date: March 6, 2012 Stamp Date: \_\_\_\_\_

Proprietary Name: Surfaxin

Established/Generic Name: lucinactant

Dosage Form: Intratracheal Suspension

Applicant/Sponsor: Discovery Laboratories

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) None
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

---

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Prevention of Respiratory Distress syndrome in premature infants

**Q1:** Is this application in response to a PREA PMR? Yes ☐ Continue  
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- ☐ Yes. Please proceed to Section D.
- ☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?\*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- ☒ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A: Fully Waived Studies (for all pediatric age groups)</b>
---

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): \_\_\_\_\_

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

			Reason (see below for further detail):				
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

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*additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification <sup>†</sup>
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

\* Other Reason: \_\_\_\_\_

<sup>†</sup> Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies.

If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

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*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_

**Q1:** Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
- ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

<b>Section A:</b> Fully Waived Studies (for all pediatric age groups)
---

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): \_\_\_\_\_
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*



**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

			Reason (see below for further detail):				
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the*

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drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies.

If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D:** Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E:** Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE **PEDIATRIC AND MATERNAL HEALTH STAFF** at 301-796-0700**

(Revised: 6/2008)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANGELA H RAMSEY  
03/02/2012

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-746 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: April 13, 2004 Action Date: February 13, 2005

HFD 570 Trade and generic names/dosage form: Surfaxin (lucinactant) Intratracheal Suspension

Applicant: Discovery Laboratories, Inc. Therapeutic Class: surfactant

Indication(s) previously approved: None

Each **approved** indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: prevention of respiratory distress syndrome (RDS) in (b) (4) \_\_\_\_\_

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☒ No: Please check all that apply: ☒ Partial Waiver ☐ Deferred ☒ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. post-birth Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. Adult Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☒ Other: only indicated for neonatal population -

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

### Section C: Deferred Studies

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

### Section D: Completed Studies

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. Neonate Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. Neonate Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Christine Yu, R.Ph.  
Regulatory Project Manager

Drafted: cyu/30 Nov 2004  
Concurrence: S Barnes/ 26 Jan 2005  
B Chowdhury/ 31 Jan 2005  
Finalized: cyu/ 31 Jan 2005

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

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Christine Yu

1/31/05 05:30:31 PM



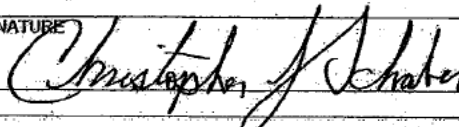
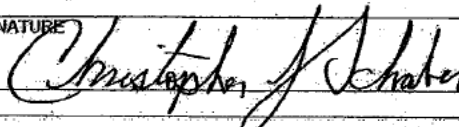
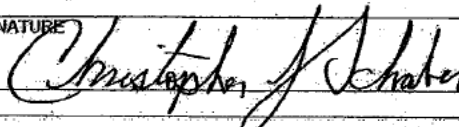


**DISCOVERY LABORATORIES, INC.**

**Debarment Certification Statement**

Discovery Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Robert J. Caporola, Ph.D.  
President/CEO  
Discovery Laboratories, Inc.

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> Food and Drug Administration		Form Approved: OMB No. 0910-0396 Expiration Date: February 28, 2006															
<b>CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS</b>																	
<i>TO BE COMPLETED BY APPLICANT</i>																	
<p>With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).</p> <div style="text-align: center; border: 1px solid black; padding: 2px; margin: 10px auto; width: fit-content;"><i>Please mark the applicable checkbox.</i></div> <p><input checked="" type="checkbox"/> (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).</p> <table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="width: 5%; text-align: center; vertical-align: middle;">Clinical Investigators</td><td style="width: 60%; padding: 5px;">See Attached List</td><td style="width: 35%;"></td></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr></table> <p><input type="checkbox"/> (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).</p> <p><input type="checkbox"/> (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.</p> <table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="width: 50%; padding: 5px;"><b>NAME</b> Christopher J. Schaber, Ph.D.</td><td style="width: 50%; padding: 5px;"><b>TITLE</b> Executive Vice President, Drug Development &amp; Regulatory Compliance</td></tr><tr><td colspan="2" style="padding: 5px;"><b>FIRM / ORGANIZATION</b> Discovery Laboratories, Inc.; 350 South Main Street, Suite 307; Doylestown, PA 18901</td></tr><tr><td style="width: 70%; padding: 5px;"><b>SIGNATURE</b> </td><td style="width: 30%; padding: 5px;"><b>DATE</b> 3/31/04</td></tr></table>			Clinical Investigators	See Attached List								<b>NAME</b> Christopher J. Schaber, Ph.D.	<b>TITLE</b> Executive Vice President, Drug Development & Regulatory Compliance	<b>FIRM / ORGANIZATION</b> Discovery Laboratories, Inc.; 350 South Main Street, Suite 307; Doylestown, PA 18901		<b>SIGNATURE</b> 	<b>DATE</b> 3/31/04
Clinical Investigators	See Attached List																
<b>NAME</b> Christopher J. Schaber, Ph.D.	<b>TITLE</b> Executive Vice President, Drug Development & Regulatory Compliance																
<b>FIRM / ORGANIZATION</b> Discovery Laboratories, Inc.; 350 South Main Street, Suite 307; Doylestown, PA 18901																	
<b>SIGNATURE</b> 	<b>DATE</b> 3/31/04																
<p style="text-align: center;"><b>Paperwork Reduction Act Statement</b></p> <p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:</p> <div style="display: flex; justify-content: space-between;"><div style="width: 60%;"></div><div style="width: 35%; text-align: right;"><b>Department of Health and Human Services</b> Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857</div></div>																	

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 21-746 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Surfaxin Established/Proper Name: lucinactant Dosage Form: Intratracheal Suspension		Applicant: Discovery Laboratories Agent for Applicant (if applicable):
RPM: Angela Ramsey		Division: Pulmonary, Allergy, and Rheumatology Products
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)            Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </div> <div style="width: 50%;"> <p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p> <input type="checkbox"/> This application does not rely upon a listed drug.  <input checked="" type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)         </p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p> <input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: 3/6/12         </p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> </div> </div>		
♦ Actions <ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>March 6, 2012</u></li> <li>Previous actions (specify type and date for each action taken)</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  <input type="checkbox"/> None    4/17/09-CR; 5/1/08 AE, 3/31/06-AE; and 2/11/05-AE

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?          Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>3</sup></p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority          Chemical classification (new NDAs only):</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><input type="checkbox"/> Fast Track  <input type="checkbox"/> Rolling Review  <input checked="" type="checkbox"/> Orphan drug designation</p> </div> <div style="width: 45%;"> <p><input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Direct-to-OTC</p> </div> </div> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>NDAs: Subpart H  <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I  <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> </div> <div style="width: 45%;"> <p>BLAs: Subpart E  <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H  <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required</p> </div> </div> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<p>• Press Office notified of action (by OEP)</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• [505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
• [505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*

### CONTENTS OF ACTION PACKAGE

- ❖ Copy of this Action Package Checklist<sup>4</sup>

#### Officer/Employee List

- ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (*approvals only*)

☒ Included

Documentation of consent/non-consent by officers/employees

☒ Included

#### Action Letters

- ❖ Copies of all action letters (*including approval letter with final labeling*)

Action(s) and date(s) 3/6/12-pending; 4/17/09-CR; 5/1/08 AE, 3/31/06-AE; and 2/11/05-AE

#### Labeling

- ❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

- Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.
- Original applicant-proposed labeling
- Example of class labeling, if applicable

2/9/12

9/6/11

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.



❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
• Most-recent draft labeling	2/16/12
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) ( <i>indicate date(s)</i> )	Acceptable
• Review(s) ( <i>indicate date(s)</i> )	1/23/12
• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 1/24/12 <input checked="" type="checkbox"/> DMEPA 1/23/12-Acceptable <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 1/13/12-Acceptable <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) 2/13/12
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input type="checkbox"/> Not a (b)(2) 3/2/12
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input type="checkbox"/> No
○ If yes, Center Director's Exception for Review memo ( <i>indicate date</i> )	
○ If yes, OC clearance for approval ( <i>indicate date of clearance communication</i> )	<input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> )	
• Date reviewed by PERC _____ If PERC review not necessary, explain: <u>No PERC review required for this NME since they received Orphan Designation</u>	
• Pediatric Page/Record ( <i>approvals only, must be reviewed by PERC before finalized</i> )	<input type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.



❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	3/2/12, 2/28/12, 2/13/12; 2/9/12; 1/19/12; 12/23/11; and 10/6/11
❖ Internal memoranda, telecons, etc.	1/27/12; 1/6/12; 12/29/11, and 10/27/11
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> N/A or no mtg 6/2/09
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	teleconferences 9/16/11 and 7/14/10
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/6/12
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/5/12
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 3/6/12
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	3/5/12
• Clinical review(s) <i>(indicate date for each review)</i>	3/5/12
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i>	
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	
• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	<input checked="" type="checkbox"/> None

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 2/28/12, 2/13/12
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 2/28/12, 2/13/12, 1/11/12, and 12/14/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None requested 1/13/12
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 3/5/12 & 2/13/12
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	<input type="checkbox"/> Not needed 2/7/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )(all original applications and all efficacy supplements that could increase the patient population)	
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: 3/2/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**Date:** March 2, 2012

<b>To:</b> Russell Clayton	<b>From:</b> Angela Ramsey Project Coordinator
<b>Company:</b> Discovery Laboratories	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 215-488-9470	<b>Phone number:</b> 301-796-2284

**Subject:** NDA 21-746 Surfaxin Draft label comments

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**Total no. of pages including cover:**

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**Comments:**

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**Document to be mailed:** YES XNO

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(301) 827-1050. Thank you.

NDA 20-746

We have the following additional label comments based on the label responses you submitted on February 23, 2012 and February 29, 2012.

### **Prescribing Information: Contents**

For section 5.3 the word “serious” was inserted to make it consistent with the rest of the label

### **Section 11 Description**

We have:

- Replaced the proposed API structures with more uniform and space-saving format. As the resolution of the drawings may not be optimal, may propose similar drawings of better resolution.
- Corrected Empirical Formulas for PA, DPPC and POPG Na.
- Added Molecular Weights for all APIs.
- Revised names for sinapultide and PA.

### **Section 14 Clinical Studies**

#### **14.1 Prevention of Neonatal Respiratory Distress Syndrome**

We have reconsidered including language that describes exploratory analyses which compare the efficacy of Surfaxin to beractant. We do not believe we can achieve a fair balance in any type of description of the data and have decided not to include efficacy comparisons between Surfaxin and beractant. This is consistent with the labels of other products regulated by the Division in which active comparators have been included in Phase 3 trials as benchmarks.

Please submit revised labeling incorporating the changes shown in the attached marked up label for the Package Insert via email or fax to Angela Ramsey by March 5, 2012. The email or fax should be followed by an official submission to the NDA.

Drafted by: AR/March 2, 2012

Initialed by: SB/March 2, 2012; TD/March 2, 2012; JN/March 2, 2012

Finalized: AR/March 2, 2012

14 PAGES OF DRAFT LABELING HAS BEEN WITHHELD IN FULL AS b4 (CCI/TS)  
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/s/  
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ANGELA H RAMSEY  
03/02/2012





Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**Date:** February 28, 2012

<b>To:</b> Russell Clayton	<b>From:</b> Angela Ramsey Project Coordinator
<b>Company:</b> Discovery Laboratories	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 215-488-9470	<b>Phone number:</b> 301-796-2284

**Subject:** NDA 21-746 (Surfaxin) IR fax # 3

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**Total no. of pages including cover:**

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**Comments:**

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(301) 827-1050. Thank you.

NDA 20-746

We note your proposed changes in Section 14.1 Clinical Studies outlined in your label

(b) (4)

[REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

As a result of the reasons mentioned above, we included a generalized statement of efficacy which would inform/reassure physicians that Surfaxin performed similarly to an efficacious surfactant product which is currently marketed.

(b) (4)

[REDACTED]

Please submit response via email or fax to Angela Ramsey by COB March 1, 2012. The email or fax should be followed by an official submission to the NDA.

Drafted by: AR/February 28, 2012  
Initialed by: SB/February 28, 2012; TD/February 28, 2012

Finalized: AR/February 28, 2012

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/s/  
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ANGELA H RAMSEY  
02/28/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**Date:** February 17, 2012

<b>To:</b> Russell Clayton	<b>From:</b> Angela Ramsey Project Coordinator
<b>Company:</b> Discovery Laboratories	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 215-488-9470	<b>Phone number:</b> 301-796-2284

**Subject:** NDA 21-746 Draft label comments

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(301) 827-1050. Thank you.

NDA 20-746

The Division has reviewed your submission dated, February 9, 2012 and we have the following comments. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

Comment 1:

Addition of the words “Up to” in the Highlights of Prescribing Information is acceptable.

Comment 2:

Use of “per” instead of the slash mark when referring to “per kg” is acceptable.

Comment 3:

Deletion of the words

(b) (4)

Comment 4:

We are in agreement.

Comment 5:

We are in agreement.

Comment 6:

(b) (4)

Comment 7:

Use of case report form adverse reaction data for both studies described in Table 3 is acceptable.

Comment 8:

In order to add context to the predefined adverse reactions in Table 2, information regarding hypoxia and bradycardia were added in the text describing administration-related adverse reactions.

Comment 9:

To comply with the Physician's Labeling Rule, the correct heading for section 6.1 is "Clinical Trials Experience". Subsequent studies to be described follow as non-numbered subheadings.

Comment 10:

We are in agreement.

**Additional FDA comments**

Comments that pertain to the entire label:

Additional changes have been made in order to bring the label more in compliance with the newer PLR format requirements. These include:

- Removal of non-required "bolding"
- Avoiding the use of the tradename of marketed products used as comparators in clinical studies
- Inclusion of a description of "Study 2" in Section 14 (Clinical Studies section) of the label

Section 6: Adverse Reactions

Subheading 6.1

- Table 2: (b) (4)  
This is because for the purposes of the study, the terms described (ETT reflux, pallor, etc.) in the table were by definition adverse reactions. Inclusion of the row listing the number of the administration-related adverse reactions reported as adverse reactions is thus (b) (4).
- The data for all-cause mortality was deleted as RDS and all-cause mortality are efficacy endpoints and are addressed in Table 4.
- The description of the "Clinical Study in Adults with ARDS" has been expanded to acknowledge it was a 2-part study.

Section 11 Description

- Insert the structures and empirical formulae of the main active ingredients of SURFAXIN (sinapultide, DPPC, POPG, Na, and, PA).

Please submit revised labeling incorporating the changes shown in the attached marked up label for the Package Insert via email or fax to Angela Ramsey by February 24, 2012. The email or fax should be followed by an official submission to the NDA.

Drafted by: AR/February 17, 2012

Initialed by: SB/February 17, 2012; TD/February 17, 2012

Finalized: AR/February 17, 2012

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ANGELA H RAMSEY  
02/17/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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## FACSIMILE TRANSMITTAL SHEET

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**Date:** February 13, 2012

<b>To:</b> Russell Clayton	<b>From:</b> Angela Ramsey Project Coordinator
<b>Company:</b> Discovery Laboratories	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 215-488-9470	<b>Phone number:</b> 301-796-2284

**Subject:** NDA 21-746 (Surfaxin) IR fax

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NDA 20-746

In your response to FDA labeling comment #6 conveyed on January 31, 2012, for study KL4-ARDS-04, the Table 2.11.2.2D found on page 246 in Module 5, volume 1 of 6 of NDA submission dated October 31, 2007, sub-classify SAEs based on whether they occurred in the open-label (Part A) or randomized, controlled (Part B) and reference where in the NDA submission the data can be verified.

Please submit response via email or fax to Angela Ramsey by COB February 14, 2012. The email or fax should be followed by an official submission to the NDA.

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Finalized: AR/February 13, 2012

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**Date:** February 9, 2012

<b>To:</b> Russell Clayton	<b>From:</b> Angela Ramsey Project Coordinator
<b>Company:</b> Discovery Laboratories	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 215-488-9470	<b>Phone number:</b> 301-796-2284

**Subject:** NDA 21-746 (Surfaxin) Carton and vial labels

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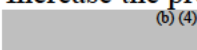
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(301) 827-1050. Thank you.

NDA 21-746

Your NDA re-submission dated, September 6, 2011, for Surfaxin (lucinactant) Intratracheal Suspension is currently under review. Comments relating to container and vial labels can be found below.

1.  (b) (4)
2. Increase the prominence of the non-proprietary name.
3. Include the "Non-pyrogenic" information to read: Sterile, Non-pyrogenic Suspension.
4. Remove the Discovery Labs logo from the vicinity of drug product name (left upper corner). Increase the legibility and prominence of the composition information.
5. Increase the prominence of the Dosing and the Storage instructions. Include  (b) (4) recommendation in the Storage instruction.
6. Increase the prominence of the supplied volume (8.5 mL) and the Rx designation.

Please submit revised container and vial labels incorporating the changes shown above via email or fax to Angela Ramsey by February 23, 2012. The email or fax should be followed by an official submission to the NDA.

Drafted by: AR/February 9, 2012

Initialed by: SB/February 9, 2012; JN/February 9, 2012; PP/February 9, 2012

Finalized: AR/February 9, 2012



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ANGELA H RAMSEY  
02/09/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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Date: January 31, 2012

<b>To:</b> Russell Clayton	<b>From:</b> Angela Ramsey Project Coordinator
<b>Company:</b> Discovery Laboratories	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 215-488-9470	<b>Phone number:</b> 301-796-2284

**Subject:** NDA 21-746 Draft label

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NDA 20-746

Your NDA re-submission dated, September 6, 2011, for Surfaxin (lucinactant) Intratracheal Suspension is currently under review. Your proposed label has been extensively revised to comply with the Physician's Labeling Rule format. Comments relating to specific sections can be found below. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label.

1. Dosage and Administration Section and Dosage Form and Strengths Section:  
Use "per" instead of "slash mark" to separate doses.
2. Section 2 Dosage and Administration  
 (b) (4)
3. 2.2 Dosing: The labeled dose of Surfaxin should be described as the volume of drug product (5.8 mL/kg) rather than as milligram quantities.
4. Section 6 Adverse Reactions  
6.1 Clinical Studies in Premature Infants  
Table 3: Per cent values for common complications associated with prematurity have been edited based on Tables 11.4.1.2.3.A and 11.4.1.2.8.B, pages 63 and 71-72, respectively, of Volume 2 of 157 of NDA 21-746 NDA submission, July 2005. Please check the edits and other values in the table and if any further changes are made, reference the specific source within the NDA submission to support the changes.
5. 6.2 Clinical Study in Adults with ARDS: This section now contains the ARDS study information.

Please submit revised labeling incorporating the changes shown in the attached marked up label for the Package Insert via email or fax to Angela Ramsey by February 10, 2012. The email or fax should be followed by an official submission to the NDA.

Drafted by: AR/January 31, 2012

Initialed by: SB/January 31, 2012; TD/January 3, 2012; TR/January 31, 2012  
JN/January 31, 2012

Finalized: AR/January 31, 2012

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ANGELA H RAMSEY  
01/31/2012



NDA 021746

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Discovery Laboratories, Inc.  
2600 Kelly Road  
Suite 100  
Warrington, Pennsylvania 18976

ATTENTION: Russell G. Clayton Sr., DO  
Senior Vice President, Research & Development

Dear Dr. Clayton:

Please refer to your New Drug Application (NDA) dated April 13, 2004, received April 13, 2004, and your Class 2 resubmission dated September 2, 2011, received September 6, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lucinactant Intratracheal Suspension, 30 mg/mL.

We also refer to your November 11, 2011, correspondence, received November 14, 2011, requesting review of your proposed proprietary name, Surfaxin. We have completed our review of the proposed proprietary name, Surfaxin and have concluded that it is acceptable.

The proposed proprietary name, Surfaxin, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your November 11, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Angela Ramsey, at (301) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology

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/s/  
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CAROL A HOLQUIST  
01/24/2012



## Patwardhan, Swati

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**From:** Patwardhan, Swati  
**Sent:** Thursday, January 19, 2012 11:27 AM  
**To:** 'Burns, Christine'  
**Cc:** Ramsey, Angela  
**Subject:** Re: NDA 21746 Information request-January 19, 2012

Dear Christine,

We are reviewing CMC section of your pending application: NDA 21746, and request additional information as follows:

**Provide an updated list of manufacturing and testing sites for the drug product. You have listed the (b) (4) as the sole performer of the Biological Activity Testing, yet the Inspection Report audit from this site provides the (b) (4) for the (b) (4) testing site and indicates that the data analysis, interpretation and reporting of results for method DP-032 is carried at the Discovery site. Please explain and provide the name, address, and FEI number for each facility involved in this analytical method. Include the name of person responsible for each part of the method DP-032.**

Please acknowledge the receipt. We request a response by COB Friday January 25th, 2012. Let me know if it is not feasible at your end.

Thank you

Swati Patwardhan  
Regulatory Health Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Center of New Drug Evaluation and Research  
Phone: 301-796-4085  
Fax: 301-796-9748

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/s/  
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SWATI A PATWARDHAN  
01/19/2012

**MEMORANDUM**

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

**DATE:** January 6, 2012

**TO:** Christine Burns

**FROM:** Angela Ramsey

**SUBJECT:** IR fax dated, December 23, 2011

**APPLICATION/DRUG:** NDA 21-746

Angela Ramsey contacted Christine Burns and Russell Clayton to notify Discovery that per the review team, request #4 from the December 23, 2011 IR fax can be omitted. Discovery acknowledged the correction and Discovery will provide responses to the remaining requests by January 18, 2012.

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ANGELA H RAMSEY  
01/06/2012

# MEMORANDUM

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

**DATE:** December 29, 2011

**TO:** NDA 21746 File

**FROM:** Philantha Montgomery Bowen, MPH, Sr. Regulatory Project Management Officer, DPARP

**SUBJECT:** **Post-MidCycle FDA Teleconference to Communicate Application Review Status**

**APPLICATION/DRUG:** NDA 21746 Surfaxin

On December 20, 2011, the FDA initiated a teleconference for GRMPs with Discovery Laboratories, Inc. and briefly communicated that the review status of the application following the mid-cycle review meeting. The FDA communicated that the submitted bioassay data and validation information is under review. The FDA informed Discovery that labeling negotiations are anticipated to begin in late January or during the beginning of February 2012, and the PDUFA date is March 6, 2012. Discovery had no further questions or concerns that needed to be addressed at this time.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, M.P.H., RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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PHILANTHA M BOWEN  
12/29/2011



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** December 23, 2011

<b>To:</b> Russell Clayton Sr, D.O. Acting Head, Regulatory Affairs	<b>From:</b> Angela Ramsey Regulatory Project Manager
<b>Company:</b> Discovery Laboratories	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 215-488-9301	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 215-488-9470	<b>Phone number:</b> 301-796-2284
<b>Subject:</b> NDA 21746 Submission dated September 2, 2011, Information Request	

**Total no. of pages including cover:**

**Comments:** Please confirm receipt by either sending an email to [Angela.Ramsey@fda.hhs.gov](mailto:Angela.Ramsey@fda.hhs.gov) or by calling 301-796-2284

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<b>Document to be mailed:</b>	YES	<input checked="" type="checkbox"/> NO
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Discovery Laboratories  
2600 Kelly Road, Suite 100  
Warrington, PA 18976-3622

Attention: Russell G. Clayton Sr., D.O.  
Vice President, Academic and Medical Affairs

Dear Dr. Clayton:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

The review of your application is pending and we request the following information and data which are necessary to complete our review.

1. Submit the revised analytical method (DP-32) and method validation results for testing the drug product biological activity in fetal rabbits (FRBAT) after implementing the following recommendations. Refer to Report METHVAL 52, dated September 2, 2011.
  - a. Revise the acceptance criteria for drug product efficacy to NLT (b) (4)
  - b. Revise the low specific limit of drug product efficacy at post release, with particular emphasis at 12 months, to NLT (b) (4).
  - c. Revise the Z value to 2.58.
  - d. Change the description for the X and Y axes to *log KL<sub>4</sub> concentration* and *efficacy (%C<sub>RS</sub>)*, respectively. Refer to Figure 3 on page 22.
2. Provide a comparative analysis for drug product batches supporting the changes implemented to the manufacturing process in 2011. Submit release and available stability data for the recent drug product batches manufactured before (e.g., lots T1003, T1004, T1005, T1006 and T1007) and after the changes (e.g., lots T1009, T1010 and T1011). Provide comparative graphs for sinapultide, DPPC, POPG and PA assays, (b) (4) (b) (4) impurities, pH, surface tension, viscosity, particle size distribution and biological activity testing.
3. Submit revised drug product specifications with revised attributes, updated methods and tightened acceptance criteria as follows. Include supportive data analysis for the recent drug product batches to document that the proposed specifications adequately control the to-be-marketed drug product.
  - a. Tighten the acceptance criteria for individual and total, (b) (4) and (b) (4) impurities to reflect the results for the drug product batches which are representative of the to-be-marketed product.



- b. Tighten the acceptance criteria for biological activity testing to reflect results obtained with the optimized FRBAT method for the drug product batches representative of the to-be-marketed product. Based on the evaluation of recently submitted data for 11 batches with shelf life up to 12 months (b) (4) we recommend  $C_{RS}$  NLT 300 % for the stability and  $C_{RS}$  NLT 320 % for the release controls.
  - c. Include a target value for the pH attribute in the specification table.
  - d. Tighten the acceptance criteria for surface tension to reflect the results for the drug product batches which are representative of the to-be-marketed product.
  - e. Revise and tighten the acceptance criteria for drug product viscosity to include the acceptable range of values and to reflect the results for the drug product batches representative of the to-be-marketed product.
  - f. Revise the specifications for the volume in container to include the target nominal volume, target fill volume and the acceptable fill range.
  - g. Revise the specifications for particle size distribution to include the acceptable ranges for (b) (4). Tighten the proposed acceptance criteria significantly to reflect the results for the drug product batches representative of the to-be-marketed product.
  - h. Tighten the acceptance criteria for the foreign particulate matter to reflect the results for the drug product batches representative of the to-be-marketed product.
4. Provide a copy of your responses to deficiencies cited by the FDA Investigation team (Form 483, dated December 16, 2011), as a result of inspection conducted at the (b) (4) Control Laboratory for the biological activity testing of the drug product.

Please provide complete response by January 18, 2011 via email to Ms. Ramsey and submit officially as an amendment to your NDA.

NDA 21746

Drafted by: JN/December 22, 2011

Initialed by: AS/December 22, 2011; TR/December 22, 2011; JZ/December 23, 2011

Finalized by: AR/December 23, 2011

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/s/  
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ANGELA H RAMSEY  
12/23/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>				
TO:  <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Angela Ramsey</b> <b>Senior Regulatory Project Manager</b> <b>OND/DPARP 301-796-2284</b>				
REQUEST DATE November 14, 2011	IND NO.	NDA/BLA NO 21-746.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)			
NAME OF DRUG <b>Surfaxin ( lucinactant)</b> <b>Intratracheal Suspension</b>	PRIORITY CONSIDERATION <b>Priority</b>	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)  January 27, 2012			
NAME OF FIRM: Discovery Laboratories		PDUFA Date: March 6, 2012				
<b>TYPE OF LABEL TO REVIEW</b>						
<table border="0"> <tr> <td> <b>TYPE OF LABELING:</b>            (Check all that apply)  <input checked="" type="checkbox"/> PACKAGE INSERT (PI)  <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI)  <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING  <input type="checkbox"/> MEDICATION GUIDE  <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)         </td> <td> <b>TYPE OF APPLICATION/SUBMISSION</b>  <input type="checkbox"/> ORIGINAL NDA/BLA  <input type="checkbox"/> IND  <input type="checkbox"/> EFFICACY SUPPLEMENT  <input type="checkbox"/> SAFETY SUPPLEMENT  <input type="checkbox"/> LABELING SUPPLEMENT  <input type="checkbox"/> PLR CONVERSION         </td> <td> <b>REASON FOR LABELING CONSULT</b>  <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING  <input type="checkbox"/> LABELING REVISION         </td> </tr> </table>				<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION				
<b>EDR link to submission:</b> <b>\\cdsesub4\NONECTD\NDA021746\4925023\Labeling</b>						
<p><b>Please Note:</b> There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.</p>						
COMMENTS/SPECIAL INSTRUCTIONS: Please review Package Insert and Carton/Container for Surfaxin. Submission is located in DARRTS dated, September 2, 2011.  Mid-Cycle Meeting: December 7, 2011  Labeling Meetings: January 2, 2012  Wrap-Up Meeting: February 8, 2012						
SIGNATURE OF REQUESTER Angela Ramsey						

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/s/  
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ANGELA H RAMSEY  
11/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>CMC MICRO &amp; STERILITY ASSURANCE REVIEW REQUEST</b>		
TO (Division/Office): <b>New Drug Microbiology Staff</b>  <i>E-mail to:</i> <b>CDER OPS IO MICRO</b> <i>Paper mail to:</i> <b>WO Bldg 51, Room 4193</b>		FROM: Angela Ramsey OND/DPARP 301-796-2284  PROJECT MANAGER (if other than sender):		
REQUEST DATE 11/2/11	IND NO.	NDA NO. 21-746	TYPE OF DOCUMENT	DATE OF DOCUMENT 9/2/11
NAMES OF DRUG <b>Surfaxin ( lucinactant)</b>		PRIORITY CONSIDERATION Priority	PDUFA DATE March 6, 2011	DESIRED COMPLETION DATE January 6, 2012
NAME OF APPLICANT OR SPONSOR: Discovery Laboratories				
GENERAL PROVISIONS IN APPLICATION				
<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED  <input type="checkbox"/> NDA FILING REVIEW NEEDED BY: _____  <input type="checkbox"/> BUNDLED  <input type="checkbox"/> DOCUMENT IN EDR         </div> <div style="width: 48%;"> <input type="checkbox"/> CBE-0 SUPPLEMENT  <input type="checkbox"/> CBE-30 SUPPLEMENT  <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY         </div> </div> <p style="text-align: right; margin-top: 10px;">Jackets will be delivered to assigned reviewer</p>				
COMMENTS / SPECIAL INSTRUCTIONS: Discovery Laboratories submitted Class 2 Resubmission dated, September 2, 2011 for Surfaxin intratracheal suspension. Please note amendment to the product specifications were submitted October 10, 2011. Paper submission will be delivered to the assigned reviewer. Previous reviewer was Vinayak Pawar  Mid-Cycle: December 7, 2011 PDUFA Goal date: March 6, 2012				
SIGNATURE OF REQUESTER  Angela Ramsey		REVIEW REQUEST DELIVERED BY (Check one): <div style="text-align: center;"> <input type="checkbox"/> DARRTS   <input type="checkbox"/> EDR   <input type="checkbox"/> E-MAIL   <input checked="" type="checkbox"/> MAIL   <input type="checkbox"/> HAND         </div>		
		DOCUMENTS FOR REVIEW DELIVERED BY (Check one): <div style="text-align: center;"> <input type="checkbox"/> EDR   <input type="checkbox"/> E-MAIL   <input checked="" type="checkbox"/> MAIL   <input type="checkbox"/> HAND         </div>		

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/s/  
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ANGELA H RAMSEY  
11/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<b>REQUEST FOR CONSULTATION</b>	
TO (Office/Division): OSE- Nichelle Rashid			FROM (Name, Office/Division, and Phone Number of Requestor): Angela Ramsey /OND/DPARP 301-796-2284	
DATE October 21, 2011	IND NO.	NDA NO. 21-746	TYPE OF DOCUMENT	DATE OF DOCUMENT September 2, 2011
NAME OF DRUG Surfaxin ( lucinactant) Suspension		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE January 24, 2012
NAME OF FIRM: Discovery Laboratories				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST				
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS				
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL				
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> Please review Package Insert and Carton/Container for Surfaxin. Submission is located in DARRTS dated, September 2, 2011.  Labeling T-con with sponsor: February 14, 2012 PDUFA Goal Date: March 2, 2012				
SIGNATURE OF REQUESTOR			METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER	



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/s/  
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ANGELA H RAMSEY  
10/21/2011

## Patwardhan, Swati

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**From:** Patwardhan, Swati  
**Sent:** Thursday, October 06, 2011 12:16 PM  
**To:** 'rclayton@discoverylabs.com'  
**Cc:** 'Burns, Christine'; Ramsey, Angela  
**Subject:** Re: NDA21746

Dear Mr. Clayton,

We are reviewing the resubmission for NDA 21746 and request following questions/clarification:

1. Will DPPC manufactured under DMF (b) (4) be used to manufacture the drug product?
2. If so, provide the following
  - a. How does it differ from the DPPC manufactured under DMF (b) (4) ?
  - i. If it is different, how does this affect the properties of Surfaxin?
  - b. Provide a copy of a letter of authorization (LOA) from (b) (4) specifying the DMF number. The copy of the LOA submitted in the DMF is not acceptable, since there is no DMF number.
  - c. Resubmit the 356h, including DMF (b) (4) as a referenced application.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail to me will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Swati Patwardhan  
Regulatory Health Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Center of New Drug Evaluation and Research  
Phone: 301-796-4085  
Fax: 301-796-9748

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/s/  
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SWATI A PATWARDHAN  
10/06/2011



NDA 21-746

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Discovery Laboratories  
2600 Kelly Road, Suite 100  
Warrington, PA 18976-3622

Attention: Russell G. Clayton Sr. DO  
Vice President, Academic and Medical Affairs

Dear Dr Clayton:

We acknowledge receipt on September 6, 2011, of your September 2, 2011, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

We consider this a complete, class 2 response to our April 17, 2009, action letter. Therefore, the user fee goal date is March 6, 2012.

If you have any questions, call Angela Ramsey, Senior Regulatory Project Manager, at (301) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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ANGELA H RAMSEY  
09/28/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 21-746

**MEETING MINUTES**

Discovery Laboratories  
2600 Kelly Road, Suite 100  
Warrington, PA 18976-3622

Attention: Russell G. Clayton Sr. DO  
Vice President, Academic and Medical Affairs

Dear Dr. Clayton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

We also refer to the telecon between representatives of your firm and the FDA on September 16, 2011. The purpose of the meeting was to discuss proposed (b) (4).

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Ramsey RN, MSN  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Date and Time:** September 16, 2011  
**Meeting Location:** Teleconference

**Application Number:** NDA 21-746  
**Product Name:** Surfaxin (lucinactant) Intratracheal Suspension.  
**Indication:** Respiratory Distress Syndrome in Premature Infants  
**Sponsor/Applicant Name:** Discovery Laboratories

**Meeting Chair:** Badrul Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Angela Ramsey RN, MSN

**FDA ATTENDEES**

Badrul A. Chowdhury, M.D., Ph.D., Division Director  
Anthony Durmowicz, MD, Clinical Team Leader  
Kimberly Witzmann, M.D., Clinical Reviewer  
Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader  
Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer  
Prasad Peri, Ph.D., Branch Chief  
Eugenia Nashed, Ph.D. Senior Chemistry Reviewer  
Alan Schroeder, Ph.D., CMC Lead  
Angela Ramsey, RN, MSN, Senior Regulatory Project Manager

**DISCOVERY LABORATORIES**

Russell Clayton, Sr., DO, Senior Vice President, Research and Development  
George Cox, Vice President, Supply Chain  
Michelle DeCrosta, PhD., Senior Director, Analytical & Technical Support  
Timothy Gregory, PhD, Senior Director, Pre-Clinical Development  
Phillip D. Simmons, Executive Director, Biostatistics and Data Management

## BACKGROUND

Discovery Laboratories submitted a Type B meeting request dated, October 20, 2010 and July 6, 2011 to discuss their proposed (b) (4) for the prevention of respiratory distress syndrome in premature infants. Prior to granting the meeting, Discovery had several communications with the Division via email. Subsequent to these communications, the Division forwarded an Advice Letter dated, February 1, 2011. Upon receipt and review of the Advice Letter, Discovery requested to continue teleconference as requested on October 20, 2010. The teleconference was scheduled for September 16, 2011

Upon review of the background material, the Division provided preliminary comments via secure email on September 15, 2011. Discovery requested to continue with the teleconference as scheduled to clarify the clinical data needed for sNDA submission.

The content of the email is below. Any discussions that occurred during the teleconference are captured directly under the relevant response. The sponsor's questions are in ***bold italics***; the Division's response is in *italics*; and the discussion is in normal font.

## DISCUSSION

### FDA Introductory comment:

(b) (4)



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/s/  
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ANGELA H RAMSEY  
09/27/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 21-746

**MEETING MINUTES**

Discovery Laboratories  
2600 Kelly Road, Suite 100  
Warrington, PA 18976-3622

Attention: Russell G. Clayton Sr. DO  
Vice President, Academic and Medical Affairs

Dear Dr Clayton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinaftant) Intratracheal Suspension.

We also refer to the teleconference between representatives of your firm and the FDA on July 14, 2010. The purpose of the meeting was to clarify the Division's responses in May 26, 2010 fax.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Ramsey, RN, MSN  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**1**

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type C  
**Meeting Date and Time:** July 14, 2010  
**Meeting Location:** Teleconference  
**Application Number:** NDA 21-746  
**Product Name:** Surfaxin (lucinactant) Intratracheal Suspension  
**Indication:** Respiratory Distress in Preterm Infants  
**Sponsor/Applicant Name:** Discovery Laboratories  
**Meeting Chair:** Anthony Durmowicz  
**Meeting Recorder:** Angela Ramsey

**FDA ATTENDEES**

Badrul A. Chowdhury, M.D., Ph.D., Director, Division  
Kimberly Witzmann, M.D., Clinical Reviewer,  
Anthony Durmowicz, MD, Clinical Team Leader  
Angela Ramsey, RN, MSN, Senior Regulatory Project  
Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer,  
Molly Topper, Pharmacology/Toxicology Supervisor  
Eugenia Nashed, Ph.D. Senior Chemistry Reviewer  
Alan Schroeder, Chemistry Team Leader  
Jinglin Zhong, Statistics Reviewer

**DISCOVERY ATTENDEES**

Russell Clayton Sr., DO, Vice President, Research & Development, Pre-Clinical and Regulatory Affairs  
Charles F. Katzer, Senior Vice President, Pharmaceutical Operations  
Robert Segal, Senior Vice President, Clinical Research and Development, Chief Medical Officer  
Phillip Simmons, Senior Director, Biostatistics and Data Management  
Timothy Wheeler, Executive Director, Quality Operations

## BACKGROUND

Discovery submitted a Type A meeting request dated, March 4, 2010 to discuss their proposed investigational plan for validating the biological activity test assessing lucinactant activity in premature rabbits. The Division denied the meeting request, but agreed to address Discovery's questions in writing. The Division responded via fax on June 1, 2010. Upon review of Division responses, Discovery requested a teleconference to clarify Division responses. Discovery submitted a new meeting package on June 23, 2010, and a teleconference was held on July 14, 2010.

### *Introductory Comments*

*As we have discussed with you on several of occasions in our previous communications including the June 1, 2010 general advice letter, the evaluation and determination of validation of the fetal rabbit biological activity test (FRBAT) as the means to reliably assess the biological activity of lucinactant is a review issue. Since the data necessary for our evaluation is to be collected, it is premature for us to comment on specific parameters of the assay that you are proposing in your June 23, 2010 submission.*

*The efficacy endpoint of the FRBAT method should be consistent between the intended stability testing and the method validation process. You have proposed to use the specific respiratory system compliance ( $C_{RS}/\text{kg}$  in %) as the efficacy endpoint for the stability testing. You are proposing the respiratory system compliance  $C_{RS}$  (%) in the method validation. This creates an inconsistency between the stability testing method and its validation process. The inconsistency may have significant implications during the review. If you elect to use  $C_{RS}$  as the endpoint, please provide rationale and justification about the change in efficacy endpoint.*

*The following responses to your questions in the June 23, 2010 submission are relevant to the efficacy endpoint specific dynamic respiratory system compliance ( $C_{RS}/\text{kg}$  in %) only. They may not be applicable to the  $C_{RS}$  end point which may need additional discussions.*

### Discussion:

The Division clarified that Discovery must validate the FRBAT assay and link to the experimental lamb model to move forward. The Division recommended a multi-step process: (a) validate the rabbit assay and (b) upon successful validation, perform a study comparing the bioactivity of the lucinactant when assessed using the rabbit assay to that observed in the experimental lamb model with the expectation that they would perform in similar fashion.

The Division addressed inconsistencies with the rabbit assay and validation endpoints, specifically, respiratory compliance noted as  $C_{rs}$  and other times as  $C_{rs}/\text{kg}$ . Discovery clarified that all  $C_{rs}$  reflect the body mass of the animals and are corrected for body weight.

**Background:** The applicant used 3 fresh lot (1-2 month) and one past intended expiry lot (16 month). Also, 4 to 8 weeks of data in accelerated conditions (15°C and 25°C) are provided for one lot (pp. 6 and 107).

FDA Response:

*The data obtained for lot T9002 in the accelerated storage condition is a step forward in addressing our recommendations. In addition, include additional data collected for drug product stored at the label condition (e.g., 6, 9, and 12 months for lot T9002) to support the whole working range of the method. Refer to comment #2 in Jun 1, 2010, letter recommending sound data support for the mid-range activity of the drug product. Also, we note confusingly similar FRBAT results for the newly manufactured lot T9003 and 16 months old lot T8006 (Refer to Table 2 on p. 100). Please explain and add additional data points to clarify.*

*Provide full CMC data for the tested drug product lots and assess the batch to batch variability observed for FRBAT results, for example differences between T0002, T9003, T9002. Submit additional characterization data as needed.*

Discussion:

The Division would like Discovery to generate additional assay data in the mid range of values. Also, the Division would like Discovery to provide additional characterization data for the drug product to account for unexplained variability between the lots. Discovery clarified that they will provide data between 3-16 months and additional characterization data.

**Question 2:**

**Does the Division agree that Discovery should use the lower specification limit (LSL) calculated from the transformed data?**

FDA Response:

*Setting of the drug product specification is a review issue. The approach of combining data by different methods and using samples aged past intended expiry to generate a reference point for setting the acceptance criteria is not acceptable.*

Discussion:

The Division commented that the approach of combining data with two different methods will not be acceptable. The Division suggested that Discovery remove data from expired lot and submit both transformed and untransformed data and clarify which data Discovery would prefer to use. Discovery agreed to the recommendation.

**Question 3:**

**Is this evaluation satisfactory for demonstration of intermediate precision of the FRBAT method?**

FDA Response:

*No. Only one fresh lot was tested for intermediate precision. To establish the range of the assay, intermediate precision should be assessed at high, middle, and low levels. See our recommendation in Comment #2, bullet #2, of Jun 1, 2010, letter.*

*In addition, the calculation of %CV for the pooled results of two analysts should include the analyst-to-analyst variation, and should not be the simple pooled variability of the two analysts.*

Discussion:

The Division recommended testing medium and low level lots in order to cover the entire range. The Division also recommended a total %CV which included analyst to analyst variation. Discovery agreed with the Division's recommendations.

**Question 4:**

**Does the Division accept the justification for the acceptance criterion?**

FDA Response:

*No. In general, demonstrating an Accuracy for the method is to assess the bias between the average of measured values to the expected value, which is an established average of the measured values from a large number of samples. In the proposed method you use average of the measured values themselves as the expected value. This approach is not scientifically sound. Improve the assessment of the accuracy for the method to demonstrate that the bias between the measurement and the objective standard/expected value are under control. This means the assay needs some reference standard or dose-response curve to provided expected values.*

Discussion:

The Division commented that the proposed method to actually assesses precision rather than accuracy. In addition, the Division suggested Discovery construct a dose-response curve for an expected value. Discovery agreed with the Division's recommended scientific approach, but admits to difficulty with an internal standard. One of the possible approaches discussed during the teleconference included establishing a mean reference value of the assay by generating an adequate number of data points collected for the active drug product with the revised method. However, one potential problem with this approach is the lack of newly manufactured drug lots. Discovery will submit a proposal under an IND for review.

**Question 5:**

**Understanding that establishing the actual numerical value for the release and stability lower limit (LSL) is a review issue (when data are available), does the Division agree with Discovery's proposed method for determining the lower specific limits?**

FDA Response:

*No, the approach to setting regulatory acceptance criteria will be developed during review, based on the quality and variability of the data collected with fully validated method. We believe it is premature to discuss in any further detail at this point.*

Discussion:

See discussion in question #2.

**Question 6:**

**Does the Division agree that the FRBAT method has been successfully revalidated per VALPROT-72?**

FDA Response:

*No, we do not agree. This is a review issue.*

Discussion:

No discussion occurred.

**Question 7:**

**Does the Division agree that the proposed experiments and analysis outlined in Test 2 and 3 of RESPROT-10-005 rev 00 provide for a reasonable approach in answering requirements stated in the fifth bullet of Comment 2 in the Introductory Comments in the June 1, 2010 communication?**

FDA Response:

*Your proposals appear reasonable but are review issues.*

Discussion:

No discussion occurred.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21746	GI-1	DISCOVERY LABORATORIES INC	SURFAXIN (LUCINACTANT) 30MG/ML

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/s/  
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ANGELA H ROBINSON  
08/16/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Jinglin Zhong, Ph.D., Yi Tsong, Ph.D., Deputy Director, DB 6 Statistical Review Team			FROM: Eugenia Nashed, Ph.D., CMC Reviewer, ONDQA, Div. 1 Ali AlHakim, Ph.D., Branch Chief, ONDQA, Div1, Branch 2	
DATE September 16, 2009	IND NO.	NDA NO. 21-746	TYPE OF DOCUMENT NDA amendment/meeting package	DATE OF DOCUMENT Aug 5, 2009
NAME OF DRUG Surfaxin (lucinactant) Intratracheal Suspension		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE Internal meeting Sep 22, 2009 Industry meeting Sep 29, 2009
NAME OF FIRM: Discovery Laboratories, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please provide a statistical review of proposed changes to the analytical method/method validation for measuring biological activity of the drug product. Note that the current submission is applicant's response to PharmTox deficiencies and the merit of the proposed method changes is under evaluation by Dr. Luqi Pei. The applicant is planning to use the new method for evaluating the linkage between the clinical effect and the biological activity of the drug product and apply it in the new clinical protocol under evaluation by Dr. Anthony Durmowicz, so please inform the whole CMC, PT and Medical teams of your findings.  <b>Background</b> The drug product manufacturing and the analytical method is changing continuously throughout the development. The currently proposed 5-point modifications to the method are outlined on pp. 160-167 + Attachments (see scanned copies attached). The currently submitted stability data for the biological activity are the same as those submitted in May 19, 2009, amendment,				

except for new data collected for 26-month old batches (page 162 and 173), which are well beyond expiry (current specifications: 300%, 12 months). As far as CMC manufacturing the 2007 batches (T7002, -03, and -04) and 2008 batches (T8004, -05, and -06) should be comparable, however modifications to the method need to be kept in mind while evaluating the poolability of the data.

Please let me know if you need any additional information.



29-SEP-09 mtg  
briefing package...



STUREP-09-008.pdf  
(753 KB)



RESPROT-09-016.p  
df (163 KB)



VALPROT72.pdf (3  
MB)

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

☒ X MAIL

☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21746	ORIG-1	DISCOVERY LABORATORIES INC	SURFAXIN (LUCINACTANT) 30MG/ML

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/s/

EUGENIA M NASHED  
09/16/2009

ALI H AL HAKIM  
09/16/2009



NDA 21746

**INFORMATION REQUEST**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Discovery Laboratories  
2600 Kelly Road, Suite 100  
Warrington, PA 18976-3622

Attention: Russell G. Clayton Sr., D.O.  
Vice President, Academic and Medical Affairs

Dear Dr. Clayton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4)<sup>1</sup>. The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented (b) (4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

<sup>1</sup> These violations include studies conducted by (b) (4) national specific to the (b) (4) facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] (b) (4) during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

**Please respond to this query within 30 days from the date of this letter.**

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

If you have any questions, call Christine Chung, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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SANDRA L BARNES  
09/13/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

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

Attention: Marjorie Hurley, Pharm.D  
Vice President, Regulatory Affairs

Dear Ms. Hurley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

We also refer to the meeting between representatives of your firm and the FDA on June 2, 2009. The purpose of the meeting was to discuss necessary steps to be taken before NDA may be approved.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Angela Robinson, Senior Regulatory Project Manager, at (301) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Angela Robinson, RN, MSN  
Senior Regulatory Project Manager  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

## **MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** June 2, 2009  
**TIME:** 12:00 pm - 1:30 pm EST  
**LOCATION:** White Oak, Bldg 22, Conference Room 1417  
**APPLICATION:** NDA 21-746  
**DRUG NAME:** Surfaxin (lucinactant) Intratracheal Suspension  
**TYPE OF MEETING:** Type A meeting  
**MEETING CHAIR:** Badrul Chowdhury  
**MEETING RECORDER:** Angela Robinson

### **FDA ATTENDEES: (Title and Office/Division)**

Curtis Rosebraugh, M.D., Director, Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Angela Robinson, RN, MSN, Senior Regulatory Project Management Officer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Anthony Durmowicz, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Luqi Pei, Ph.D., Senior Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Molly Shea, Ph.D., Acting Pharmacology/Toxicology Supervisor, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

Ali Al-Hakim, Ph.D., Chief, Division of Pre-Marketing Assessment I, Branch II, Office of New Drug Quality Assessment

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I, Branch II, Office of New Drug Quality Assessment

Eugenia Nashed, Ph.D., Senior Chemistry Reviewer, Division of Pre-Marketing Assessment I, Branch II, Office of New Drug Quality Assessment

### **EXTERNAL CONSTITUENT ATTENDEES: Discovery Laboratories**

Russell Clayton, D.O., Vice President, Academic and Medical Affairs



Charles Katzer, Senior Vice President, Manufacturing Operations

David Lopez, Esq., Executive Vice President

Robert Segal, M.D., FACP, Senior Vice President, Medical and Scientific Affairs and Chief Medical Officer

Phillip Simmons, Senior Director, Biostatistics and Data Management

Gerald Orehostky, Senior Vice President, Quality

Marjorie Hurley, Vice President, Regulatory Affairs

## **BACKGROUND:**

Discovery submitted a Type A meeting request and background material dated, April 24, 2009, and additional data dated, May 19, 2009, to seek guidance on necessary steps to be taken before NDA may be approved for Surfaxin (lucinactant) intratracheal suspension. Upon review of the material, the Division responded via secure email on June 1, 2009. The content of the email is provided below. Discovery requested to continue with a face- to- face meeting as scheduled and requested discussion of questions 1, 5 and 10.

The content of the fax is below. Any discussion that occurred during the meeting is captured under relevant response. The sponsor's questions are in ***bold italics***; the Division's response is in *italics*; discussion is in normal font.

### **Question #1**

***Please explain the basis for stating that the results were inconsistent and the methodology used for your evaluation. Please include in your explanation the specific data set(s) used for this determination.***

### **FDA Response:**

*The results of lamb studies and rabbit biologic activity test (BAT) were inconsistent because the rabbit BAT was unable to detect an approximate 50% decrease in lucinactant activity in expired drug lots (as measured by % change in respiratory compliance) which was detected in lamb studies. Thus, the rabbit BAT has not been adequately linked to the premature lamb study(ies), which, in turn, is the animal model the Agency accepted in order for you to be able to link to the biological activity of the lucinactant used in the pivotal Phase 3 trials. This link is necessary because you failed to develop and validate an adequate lucinactant biologic activity test during lucinactant's early development and therefore did not have a method to ensure the biologic activity of subsequent lucinactant lots is consistent with that of the lots used in the clinical trial(s).*

*Table 1 provides the summary data for the evaluation. The data were extracted from the 2008 lamb study and rabbit Study RES-08-022 report. Comparisons were made on lucinactant*

activity, expiry status, dose, and animal species. Lucinactant activity was expressed as net increases (%) in respiratory compliance 30 minutes after treatments. Expiry status was determined by the respective expiration dates of the testing lots. Lots tested after their expiration dates were considered expired (i.e., T7002 and T7003). Lots that were tested before their expiration dates were not considered expired (or unexpired, i.e., Lots T8004, T8005 and T8006). It was noted that there were differences in compliance parameters and control values between the lamb and rabbit studies. These differences were not considered to impact significantly data interpretation and conclusions.

The data in Table 1 demonstrate that the premature lamb model was able to detect decreases in biologic activity (as determined by changes in lung compliance) in lots of lucinactant that had expired while the rabbit BAT was unable to detect any difference between expired and unexpired lots. Lambs treated with 5.8 mL/kg of lucinactant showed mean compliance increases of 63% and 127% in the expired and unexpired lots, respectively, which corresponds to a 50% loss of biologic activity in the expired lots. Rabbits treated with the same lucinactant dose showed no apparent difference in lung compliance between the expired and unexpired lots.

**Table 1: Effect of Lucinactant on Lung Compliance in the Lambs and Rabbits**

Lot	Expired at the time of testing	Mean Increase in Compliance (%) <sup>a</sup>		
		Rabbit <sup>b</sup>		Lamb <sup>c</sup>
		5.8 mL/kg	8.0 mL/kg	5.8 mL/kg
T7002, T7003	Yes	403	238	63
T8004, T8005, T8006	No	416	377	127
Mean	-	411	341	-

a. Increases (net) in lung compliance 30 minutes after intratracheal instillation of lucinactant. These numbers were obtained by subtracting 100 from the reported percentage values (%).

b. Increases (%) over negative (air) control groups in specific dynamic lung compliance measured in  $C_{RS}$ /kg from Study RES08-022. The mean of 403% for expired Lots T7002 and T7003 at the 5.8 mL/kg dose was derived by subtracting 100 from the reported value of 503%. Other numbers in rabbits were derived using the same approach. See Table 5 (Appendix) for reported values for respective doses.

c. Increases (%) over baseline in lung compliance measured in mL/cm H<sub>2</sub>O/kg from the 2008 lamb study. See Tables 2 and 4 (Appendix) for data set for deriving these numbers.

In addition, data generated in the premature lamb has been consistent over time. There were a total of 3 lamb studies, including the 2008 study, from two laboratories over a period of 3 years. All studies used the same lucinactant dose of 5.8 mL/kg. Both previously completed (2007 and literature) studies used unexpired lots while the 2008 study used both expired and unexpired lots. Table 2 summarizes the results of these studies. The efficacy of unexpired lucinactant lots was consistent across the laboratories over the period of 3 years; 127% to 178% increases in compliance and was also consistent with the published data by Gastiasoro- Cuesta et al (the study which the Agency agreed could be used to provide a link to the biologic activity of lucinactant used in the pivotal clinical trials. Importantly, the same lots (T7002 and T7003) which, when assessed prior to expiration in the lamb model, had comparable activity to other

unexpired lucinactant lots (126% net increase in lung compliance) subsequently demonstrated a 50% decrease in biologic activity when expired (only a 63% net increase in lung compliance).

**Table 2: Effect of Expiry Status on Lucinactant Efficacy in Pre-Term Lambs**

Lot No./ Grouped	Date of Manu- facture	Time of Testing	Expired at Time of Testing	Mean Lung Compliance <sup>a</sup>	
				Percent of Baseline	Net Increase
T7002 T7003	1/23/07 1/31/07	Jul-2008	Yes	163.4 ± 15.0%	63%
T7002 T7003	1/23/07 1/31/07	Sep-2007	No	226.3 ± 70.3%	126%
T7004	N/A	Sep-2007	No	277.5 ± 48%	178%
T8004 T8005 T8006	5/21/08 7/16/08 7/31/08	Jul - Aug 2008	No	227 ± 14.4%	127%
N/A	N/A	Literature <sup>b</sup>	No	262.5%	162.5%

a. 30 minutes after lucinactant treatment.

b. Gastiasoro- Cuesta et al. (Pediatrics, 2006; 117:295-303).

In summary, the premature lamb model demonstrated that the unexpired lots of lucinactant had relatively consistent efficacy when assessed by different laboratories over a period of three years while expired lots had significant drops in lucinactant biologic activity when tested in the same manner at the same time. The rabbit BAT, however, did not detect any loss of lucinactant activity between the expired and unexpired lots. Taken as a whole, the data demonstrate the inability of the rabbit BAT to detect the significant decreases in lucinactant biologic activity observed between expired and unexpired lots of lucinactant and, thus, fail to link the ability of the rabbit BAT to assess biologic activity of lucinactant to that of the premature lamb studies.

#### Discussion:

The sponsor stated that the goal in 2006 was to refine their rabbit animal model (rabbit BAT) for use as a quality control tool for the to-be marketed product and link it to the lamb model of surfactant activity and thus demonstrate that their current drug product biological activity was consistent with that used in clinical trials. The sponsor stated that the regression analysis of lung compliance data from the rabbit and lamb data show consistency and that the rabbit BAT when used for quality control was capable of discriminating active versus inactive lots of drug product and therefore, the sponsor believes the rabbit quality control method works. The sponsor questioned what would it take for the Division to feel comfortable with it.

The Division responded by outlining the main clinical development and quality control issues pertinent to being able to consistently assess the biological activity of lucinactant, most notably, the need to demonstrate consistency of the rabbit BAT and to be able to demonstrate that it is able to differentiate active from inactive lots of drug as the lamb model is able to thereby linking the two. The Division clarified that the rabbit and lamb model should be interchangeable.

The sponsor stated that when they have analyzed the rabbit BAT data they have calculated a coefficient variation of 17% which they believe should be acceptable for such an in vivo test as the rabbit BAT. The sponsor questioned if this be an acceptable margin for the Division. The Division responded that statisticians need to analyze the data in order to make that determination.

### Question #5

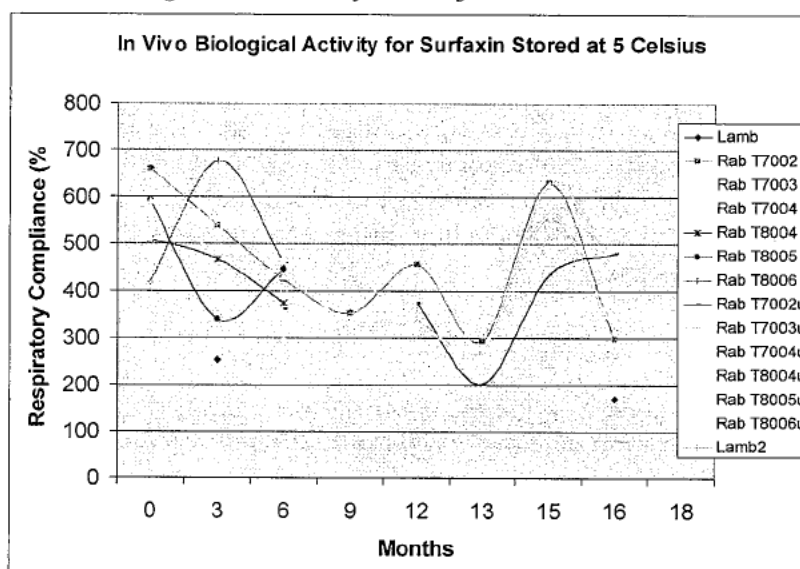
*Please explain what the Agency means by “adequately validated,” as stated in Item 1 of the Agency’s April 17, 2009 Complete Response Letter. What specific aspect(s) of the fetal rabbit BAT did the Agency determine was (were) not adequately validated and why?*

### FDA Response:

*An adequately validated method for testing lucinactant biologic activity (or potency) should follow general principles of any other quality assays. Potency is defined as improvements in respiratory compliance in the testing animals. The method should have good reproducibility and appropriate controls. The controls should yield expected results. It should at least be able to clearly differentiate lucinactant biologic activity of the testing samples according to their expiry status if the lucinactant biologic activity was used as an acceptance criterion. Expired samples/lots should show a significant drop in activity or potency when compared to the unexpired samples/lots while unexpired samples should have the same potency as other qualified batches. Further, because you failed to develop and validate an adequate lucinactant biologic activity test prior to conducting your pivotal clinical trials, you do not have a method to ensure that the biologic activity of subsequent lucinactant lots is consistent with that of the lots used in the clinical trials. The rabbit BAT should mimic the lamb model in predicting/detecting lucinactant activity batches over their shelf lives.*

*There are apparent deficiencies with the current rabbit BAT. These deficiencies have been discussed in detail in our response to Question 1. Importantly, the rabbit BAT failed to replicate the findings in the lamb model. Further, data in Figure 1 below show that the rabbit BAT cannot reproducibly or consistently detect lucinactant biologic activity in and of itself. This lack of consistency was also noted for the historical process validation lots as illustrated by the data presented in Table 3 which summarizes data provided in the April 24, 2009 submission. Note that at most time points, the 2005 PV lots at 5 °C would have apparently failed to meet the proposed acceptance criterion of (b) (4), in Method DP-32 (see highlighted values). Overall, the variability of the data suggests that either the drug is unstable, that the method is unreliable, or both.*

**Figure 1: Stability Data of Lucinactant Lots**



**Table 3: Stability Data (in vivo activity) of Lucinactant Lots**

Storage mode	Time (month)	Batches					
		2007 PV Lots (stored at 15°C)			2005 PV Lots (stored at 5°C)		
		T7002	T7003	T7004	5065202	5065204	5065206
							A
At release	0	661	555	449	298	529	347
Inverted	3	190	346	197	309	402	132
	6	102	190	193	302	485	78
	9	153	111	141	128	170	
	11					179	
Upright	3	150	159	240			
	6	131	129	128	129	252	185

**Discussion:**

The Division stated from a clinical perspective, (fig 1) shows a decrease in respiratory compliance over time, but the data at 13 month data shows an increase; therefore, the Division questioned if something is going on with the product, or if the method is not reliable. The sponsor acknowledged that outliers exist and the data at 15/16 months was not the results they had expected and the analysis would be problematic. The sponsor stated that they developed a stability model with upper and lower limits of acceptance as a quality control tool in order to ensure lot to lot consistency in the drug product.

The Division asked the sponsor to clarify what dosing was used for data collected in 2007 and 2008, and whether there was any overlapping data available for the two dosing regimens.

The sponsor proposed to conduct another lamb study concurrent with the rabbit BAT, both dosed at 5.8 mL/kg, to again attempt to demonstrate comparability between the two biological activity tests and, thus, link the two models/assays. The Division responded by stating that in order to link the rabbit and lamb models of determining biological activity, they saw no other way but to repeat lamb and rabbit studies but then stated that it may not be possible to adequately link the two tests. The Division then asked whether the sponsor had considered conducting clinical trials with the new PV lots of lucinactant as a path forward to approval rather than trying to link the two assays of biological activity. The sponsor stated that for financial purposes, a full clinical development plan was not an option. The Division stated that it may be possible that a more limited development plan would suffice. The sponsor questioned what the Division meant by "limited" development plan. The Division responded by stating that our definition of "limited" may be quite different than that of the sponsor and suggested the sponsor consider their alternatives and, if interested in pursuing conducting further clinical trials, they should submit a new development plan for comment.

**Question #10**

*If upon approval the Agency determines that the approval was based in part on published literature to which Discovery has not obtained a right of reference to the raw data underlying the published study or studies, what are the practical consequences of approval pursuant to*

*section 505 (b)(2) that are different from approval of the application pursuant to section 505 (b)(1)?*

FDA Response:

*Because the published report by Gastiasoro-Cuesta, et al. (Pediatrics, 2006; 117:295-303) acts as a link to the biologic activity of lucinactant utilized in pivotal Phase 3 trials, the NDA should be submitted under section 505 (b) (2). That said, we do not understand what you mean by the “practical consequences” of such an application. Please specify any particular concerns you have regarding such a submission.*

Discussion:

The sponsor asked the Division to clarify if there would be any differences in the way the NDA would be reviewed or consequences of approval under the 505(b)(2) approach.

The Division stated that to its knowledge there would be no differences how the submission would be handled if submitted under the 505(b)(2) path compared to if submitted under 505(b)(1).

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

There were no issues requiring further discussion.

**ACTION ITEMS:**

No action items for this meeting

**ATTACHMENTS/HANDOUTS:**

During the meeting, sponsor provided additional copies of the figures from the amendment dated May 19, 2009.

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/s/

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Angela Robinson  
6/16/2009 09:44:53 AM

## MEMORANDUM OF TELECON

DATE: March 4, 2009

APPLICATION NUMBER: NDA 21-746

BETWEEN:

Name: Marjorie Hurley  
Phone: 215-488-9360  
Representing: Discovery Labs

AND

Division of Pulmonary and Allergy Products:

Name: Badrul Chowdhury, Division Director  
  
Anthony Durmowicz, Medical Officer  
  
Luqi Pei, Pharmacologist/ Toxicologist Reviewer  
  
Timothy Robison, Pharmacologist/Toxicologist Lead  
  
Eugenia Nashed, Chemistry Reviewer  
  
Prasad Peri, Chemistry Team Lead

SUBJECT: To update Discovery on the status of the review of NDA 21-746

This is a memo to file regarding an informational telephone conversation on March 4, 2009 with Discovery representatives to update them on the status of the review of NDA 21-746. No meeting minutes were taken.

The Division indicated that there are potential issues with linking the proposed rabbit assay with the lamb model, which was never validated. The Division stated that this matter needs to be resolved; therefore, there will be no additional discussion including labeling until the action letter.

Discovery asked whether there is any additional information that they could provide to assist the Division. The Division responded that no additional information is required at the present time.

Discovery acknowledged the Divisions comments and appreciated the Division's feedback.



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SIGNER'S NAME

TITLE

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/s/

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Angela Robinson  
3/9/2009 10:14:45 AM  
CSO



**FOOD AND DRUG ADMINISTRATION**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

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Meeting Type: C

Meeting Category: End-of Review

Meeting Date: June 18, 2008

Time: 12:00pm- 1:00pm

Meeting Location: Teleconference

Product Name: Surfaxin (lucinactant)

Application: NDA 21-746

Sponsor: Discovery Laboratories

Meeting Requestor: Marjorie Hurley

Meeting Recorder: Angela Robinson

**DISCOVERY LABORATORIES REPRESENTATIVES:**

Marjorie Hurley, PharmD., VP, Regulatory Affairs  
David Lopez, Esq., Executive VP  
Gerald Orehostky, Sr. VP, Quality Operations  
Robert Segal, M.D., Sr. VP, Medical and Scientific Affairs and Chief Medical Officer  
Laura Grablutz, Sr. Director, Regulatory Affairs  
Michelle DeCrosta, Sr. Director, Technical and Analytical Services  
Phillip Simmons, Sr. Director, Biostatistics  
Brian Boyd, Director Process Engineering

**DIVISION OF PULMONARY AND DRUG PRODUCTS (DPAP) REPRESENTATIVES:**

Badrul A. Chowdhury, M.D., Ph.D., Division Director  
Sally Seymour, M.D., Clinical Team Leader  
Anthony Durmowicz, MD, Clinical Reviewer  
Huiqing Hao, Pharmacology/Toxicology Reviewer  
Timothy McGovern, PhD, Pharmacologist/Toxicologist Team Leader  
Angela Robinson RN, MSN, Senior Regulatory Project Manager

**Office of New Drug Quality Assessment, Division of Pre- Marketing Assessment I**

Prasad Peri, PhD, Pharmaceutical Assessment Lead

Eugenia Nashed, PhD, ONDQA Reviewer

**New Drug Microbiology Staff**

Vinayak Pawar PhD, Microbiology Reviewer

**Background**

Discovery submitted a meeting request dated, May 14, 2008 requesting an End-of-Review meeting to discuss the May 1, 2008, Approvable letter. A briefing package with questions was included with the meeting request. In a faxed dated, June 17, 2008 the Division provided responses to Discovery's questions. A teleconference was held on June 18, 2008 to further clarify the Division's comments. The faxed contents are below. Any discussion that took place during the meeting is captured directly below the original response. Discovery's questions are in ***bold italics***; the Division's response is in *italics*; the discussion is in normal font.

***9.1 Clarification Related to the Fetal Rabbit Biological Activity Test Method (DP-018) and Validation (Comment 14)***

**Question 1a:**

***Does the agency agree that the volume /weight (dose) for the test article and positive control used in method DP-018 are justified and acceptable?***

**FDA Response to Question 1a:**

*No. Your arguments do not justify using the 8 mL/kg lucinactant volume in the rabbit bioactivity assay. The rabbit model is intended to replace the original lamb model in measuring lucinactant product activity and, therefore, should mimic the clinical setting in the initial validation process. As noted in the meeting of December 21, 2006, lucinactant should show comparable bioactivity between the rabbit and lamb models. This comparable bioactivity cannot be verified if different dosing procedures are used. Additionally, your use of a dosing volume of 5.6 mL/kg for Survanta in the rabbit study does not support your statement that a volume of 8 mL/kg was chosen to ensure the accurate administration of a very small volume. We recommend the use of a dosing volume of 5.8 mL/kg lucinactant in rabbit bioactivity assay. Once the link between the two models is characterized, you could then provide a bridge with in the rabbit model for the two dosing volumes if desired.*

**Discussion:**

Discovery stated that they believe that they have established a relationship between the lamb and rabbit models. They believe that using the 8 mL/kg lucinactant volume in the rabbit bioactivity assay is justified because the rabbit model was optimized at this volume and it will not act as clinical surrogate to monitor quality of drug product. Rather it will be used for quality control and is considered valid as long as it can differentiate the active

and the inactive drug. The 5.8 mL/kg was used in the preterm lamb study because the preterm model is specifically designed to mimic the clinical setting.

The Division reminded Discovery that during the conduct of their clinical trials they never linked the activity of Surfaxin drug lots used in the pivotal clinical trial to a bioassay which would then be used to monitor quality control. The only bioassay link available to the clinical lots was data from a fetal lamb research study that assessed changes in the lung mechanics upon administration of lucinactant (Pediatrics 2006, vol 117: 295-303). The Division agreed to allow the data from the fetal lamb research paper to be the link to the original clinical study lots used in the pivotal study and stated that another lamb study should be carried out using the same methodology as that in the research paper and should include a side by side comparison of the lamb and rabbit bioassay, the results of which, if consistent, could be used to bridge the activity of the current drug batches to the clinical batches. The rabbit assay could then replace the lamb study results as the bioassay moving forward.

Additionally, at the December 21, 2006, meeting with Discovery, the Division stated that the comparative data should be reproducible, i.e., at least three test for each of the three newly made batches should show similar results. Alternatively, Discovery could perform another clinical trial using batches tested in the rabbit bioassay as a way to move development forward.

Discovery stated that they have tested three batches in rabbit model and the data were submitted in the response to the approvable letter of October 31, 2007 and the data validated the rabbit model. The Division indicated that the validation study report included the data from the test of one batch only. Discovery asked if data from the of rabbit model with three batches, using 8 mL/kg will be adequate to validate the rabbit model. The Division responded that the data generated with doses of 8 mL/kg in rabbit model is not acceptable to serve the link between the rabbit model and lamb model. The Division clarified that the data from the same three batches tested in rabbit and lamb models with the same dose, 5.8 mL/kg are needed. Discovery stated that they did not believe that this type of comparison was necessary but that it was more appropriate to compare the two volumes in the rabbit model. The Division stated that Discovery could pursue that approach at their own risk and could submit what they believe is an appropriate response and the Division will review it.

**Question 1b:**

***Does the agency agree that the method of determining the appropriate acceptance criterion (threshold) for each lot of Survanta used as positive control system suitability is acceptable?***

**FDA Response to Question 1b:**

***No. Your proposal to set an acceptance criterion on a lot-by-lot basis is not acceptable because that approach does not provide assurance that the rabbit model may be conducted in a reproducible manner since different batches could potentially produce a wide range of responses. We recommend that you test an adequate number (at least 3) of***

*Survanta batches to establish a general acceptance criterion for the selected positive control.*

*Justify using natural log-transformed data to determine the acceptance threshold instead of using the mean %Crs data.*

Discussion:

No discussion occurred.

**Question 1c:**

***Does the Agency agree that the proposed acceptance criterion (b) (4) of air control for lucinactant drug product tested in method DP-018 is justified by the data and acceptable?***

**FDA Response to Question 1c:**

*No. We do not agree with your proposal. Provide detailed test reports including study objectives, methods and results for at least three lots of lucinactant to support your proposal. Although your briefing package for this meeting refers to data from three PV lots, to date, you have submitted only summary information pertaining to Lot T7004 for our review.*

*In addition, refer to the response to Question 1b regarding our comments on the use of data transformation methods in setting the acceptance criterion for a positive response.*

Discussion:

No discussion occurred.

**Question 1d:**

***Does the agency agree that the inclusion of a single lot of biologically active Surfaxin in the validation of method DP-018 was appropriate and acceptable?***

**FDA Response to Question 1d:**

*No. The rabbit bioactivity test is to be used to ensure that future batches show adequate biological active. Data from at least three batches of Surfaxin are needed to validate the rabbit model in comparison to the lamb model and establish appropriate positive acceptance criteria.*

*Provide a complete study report including purpose, method and result (summary and individual data) for each section as recommended in comment 14.b.3) in the letter of May 1, 2008.*

Discussion:

See Discussion 1a.

**9.2 Clarifications Related to Limits of Impurities in Drug Substances (Comment 11b)**

**Question 2:**

***Does the agency agree that the proposed limits on lipid- related impurities in the three lipid drug substances are acceptable?***

**FDA Response to Question 2:**

*We are unable to provide a definitive answer at this time. Based on your statement that all impurities above 0.1% have been identified and are endogenous to humans, provide the individual chemical names, structures and details of the calculations determining their endogenous levels in terms of mg/g lung tissue and concentration in surfactant (incorporating the total volume of surfactant in the lung and the amount of these "impurities" in surfactant). Note that a safety evaluation based on the percentage of an impurity as a proportion of the total lipid pool as in Table 4 (page 11 of the May 14, 2008 submission) is not acceptable. If you intend to use the ferret toxicity study to support the safety of any drug substance related impurities, provide the individual chemical names, structures and details of the calculations determining the ferret exposure on a mg/g lung tissue basis. In general, a 10-fold margin of safety is expected for impurity qualification although deviations may be acceptable with adequate information supporting the endogenous nature and observed levels of the impurities.*

*We note that (b) (4) of lung surfactant, based on the data provided in Table A on page 4 of the June 3, 2008 submission. The acceptability of the actual specification limits (expressed as percentage of each drug substance rather than as a percentage of the lipid pool) will be a review issue. Submit supporting release and stability data from the recent batches. Tighten the acceptance criteria for unknown and unspecified impurities. The recommended ICH threshold is 0.10% for identification and 0.05% for reporting.*

**Discussion:**

Discovery asked why their proposal to report each impurity as a percentage of the total lipid pool rather than as a percentage of each drug substance is not acceptable.

The Division stated that for the synthetic drug products, all existing regulatory guidance defines impurities as a percentage of the drug substance they are derived from rather than a percentage of all drug substances present in the drug product formulation. If Discovery has data documenting that the same chemical entity is formed from two different drug substances it should submit it for review in support for any special considerations.

The Division reiterated that the comparison between the impurity exposure and the endogenous level need to be on a mg/g lung weight basis and should consider the relevant indicated age groups. Comparisons based on percentages do not adequately address the safety questions.

**9.3 Clarifications Related to the Limit of (b) (4) in Drug Product (Comment 13 c)**

**Question 3:**

***Does the agency agree that a drug product limit of (b) (4) impurity is acceptable?***

FDA Response to Question 3:

*We are unable to provide a definitive answer at this time. Provide a chemical name and structure, including characterization information (e.g. identification of drug substance from which (b) (4) is derived), for the (b) (4) degradation impurity and details of the calculations used to determine its endogenous level in terms of mg/g lung tissue and/or surfactant.*

*Calculate safety margins based on the comparative animal to human lung burden (mg/g lung tissue in ferrets ÷ mg/g lung tissue in humans). In general, a 10-fold margin of safety is expected for impurity qualification although deviations may be acceptable with adequate information supporting the endogenous nature and the observed level of the impurity.*

Discussion:

The Division asked Discovery to provide a chemical name molecular weight and structure, including characterization and origin information, for the (b) (4) degradation impurity. The Division asked Discovery to clarify the lipid from which the (b) (4) impurity is derived.

**9.5 Clarification Related to the (b) (4) Overfill of Drug Product (Comment 13 d)**

Question 5:

*Does the agency agree that the (b) (4) overfill is justified? If not, do you agree that the alternative proposal of restating the label claim as (b) (4) is acceptable?*

FDA Response to Question 5:

*The (b) (4) drug product overfill is not justified, unless adequate supportive data are provided. Specify the extractable volume of the drug product, when extracted under the conditions described in the labeling. No data regarding this was provided in the application. As requested in comment 13.d. of the May 1, 2008, letter, provide revised drug product specifications stating the target volume (b) (4) data-based acceptable volume range and the nominal fill volume (b) (4). The nominal volume should be consistent with the drug product labeling.*

Discussion:

Discovery questioned whether the nominal fill volume should be listed in the package insert. The Division recommended that the label content in SPL be consistent with the draft labeling for the package insert.

**9.7 Clarification Regarding the Inclusion of the Composition of the Drug Product on the Vial and Carton Labels (Labeling Comment 2a)**

Question 7:

*Is the addition of the proposed statement on the vial acceptable to the agency?*



FDA Response to Question 7:

No. Redesign the vial label to provide basic composition information. Include, at the minimum, correct concentrations of total phospholipids AND synthetic peptide. Submit revised mock-up labels for detailed comments with the NDA resubmission. Explain why the total amount of phospholipids is different in your meeting package dated May 14, and June 3, 2008 (e.g., page 9), and in the proposed label revisions.

In addition, provide information/data regarding the integrity of the label and its adhesion to the vial surface upon exposure to the 44 °C (b) (4), as defined in the proposed label.

Discussion:

Discovery asked the Division to clarify what is meant by the term total amount of phospholipids. The Division recommended submitting redesigned labeling with specific composition information for detailed comments. The labeling should include correct numbers for the content of total lipids, phospholipids and peptide. Include data supporting the integrity of the drug product and the label during the warming process as defined in the labeling. (b) (4) Discovery agreed to submit a redesigned label.

Discovery commented that the preparation of the product prior to administration does not (b) (4) therefore, label adhesion is not a problem. Discovery asked whether the Division still requires data regarding label adhesion. The Division stated that general information is required to ensure that users do not expose the label to high temperatures, therefore; the Division recommended studying the effect of submersion of the vial in a (b) (4) on label adhesion.

Drafted By: Robinson/ June 23, 2008  
Initialed by: Durmowicz/July 11, 2008  
Seymour/July 14, 2008  
Nashed/June 24, 2008  
Peri/June 24, 2008  
Al Hakim/June 24, 2008  
Hao/ June 24, 2008  
McGovern/June 30, 2008  
Pawar/ June 24, 2008  
Chowdhury/July 14, 2008  
Finalized by: Robinson/July 14, 2008

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/s/

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Angela Robinson  
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5/20/08



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

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

Attn: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs

Dear Dr. Hurley:

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

We also refer to your May 14, 2008, correspondence, received May 15, 2008, requesting an End-of-Review meeting.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: June 18, 2008  
Time: 12:00pm-1:00pm EST  
Phone Arrangements: Please provide the call-in number and passcode at least 24 hours prior to the meeting.

CDER Participants:

Office of Drug Evaluation II

Curt Rosebraugh, MD, MPH, Office Director  
Leah Ripper, Associate Director of Regulatory Affairs

Division of Pulmonary and Allergy Products

Badrul Chowdhury, MD, PhD, Division Director  
Sally Seymour, MD, Clinical Team Leader  
Tony Durmowicz, MD, Clinical Reviewer  
Angela Robinson, RN, Sr. Regulatory Management Officer  
Tim McGovern, PhD, Pharmacology/Toxicology Team Leader  
Haoqing Hao, PhD, Pharmacology/Toxicology Reviewer

Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I

Ali Al Hakim, PhD, Chief, Branch II

Prasad Peri, PhD, Pharmaceutical Assessment Lead  
Eugenia Nashed, PhD, ONDQA Reviewer

New Drug Microbiology Staff

Vinayak Pawar, PhD, Microbiology Reviewer  
David Hussong, PhD, Microbiology Team Leader

If you have any questions, call LCDR Angela Robinson, Sr. Regulatory Management Officer at (301) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Sincerely,

*{See appended electronic signature page}*

Lori Cantin, RPh  
Senior Regulatory Management Officer  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Lori Cantin  
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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

**Memorandum of Facsimile Correspondence**

Date: April 25, 2008

To: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs  
Discovery Laboratories, Inc

Fax:

Phone: (215) 488-9360

From: Lori Cantin, R.Ph.  
Senior Regulatory Management Officer  
Division of Pulmonary and Allergy Products

Subject: FDA-revised labeling/NDA 21-746/Surfaxin

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Thank you.

NDA 21-746

Discovery Laboratories, Inc.  
2600 Kelly Road, Suite 100  
Warrington, PA 18976

Attention: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs

Dear Dr. Hurley:

Please refer to your April 13, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

As discussed at the labeling teleconference on April 24, 2008, we are providing the FDA-revised labeling for Surfaxin (attached below). FDA-proposed insertions to the PI are underlined and deletions are in strike-out. We feel this version of the label is accurate and offers fair balance to your product. Note that after internal discussion, we are open to alternative language in two areas of the CLINICAL STUDIES section discussed during the teleconference; the geographic description of where the trials were conducted, and the

(b) (4)

Submit alternative language for the two areas of the CLINICAL STUDIES section indicated above. We request that you submit your proposed draft labeling by April 29, 2008.

Also, include a footnote to Table 2 explaining the difference in group patient numbers.

Other than the changes recommended above, we do not feel that any other substantial changes in the label are necessary.

If you have any questions, call Lori Cantin, Senior Regulatory Management Officer, at 301-796-1212.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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/s/

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Lori Cantin  
4/25/2008 12:54:55 PM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

**Memorandum of Facsimile Correspondence**

Date: April 14, 2008

To: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs  
Discovery Laboratories, Inc

Fax:

Phone: (215) 488-9360

From: Lori Cantin, R.Ph.  
Senior Regulatory Management Officer  
Division of Pulmonary and Allergy Products

Subject: FDA-revised labeling/NDA 21-746/Surfaxin

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Thank you.

NDA 21-746

Discovery Laboratories, Inc.  
2600 Kelly Road, Suite 100  
Warrington, PA 18976

Attention: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs

Dear Dr. Hurley:

Please refer to your April 13, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinaftant) Intratracheal Suspension.

We also refer to your submission dated October 31, 2007.

The Division's comments regarding the proposed labeling are provided, followed by our proposed revisions to the labeling submitted on November 12, 2007. FDA-proposed insertions to the PI are underlined and deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

We request that you submit your revised draft labeling and/or comments within 1 week of the date of this facsimile.

If you have any questions, call Lori Garcia, Senior Regulatory Management Officer, at 301-796-1212.

## **LABELING COMMENTS**

(b) (4)



(b) (4)



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/s/

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Lori Cantin  
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CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Office/Division): <b>Division of Drug Marketing, Advertising and Communications</b>			FROM (Name, Office/Division, and Phone Number of Requestor): <b>Lori Garcia, R.Ph., Regulatory Project Manager</b> <b>Division of Pulmonary and Allergy Products</b>	
DATE <b>February 25, 2008</b>	IND NO.	NDA NO. <b>NDA 21-746</b>	TYPE OF DOCUMENT <b>Original NDA</b>	DATE OF DOCUMENT <b>October 31, 2007</b>
NAME OF DRUG <b>Surfaxin</b>	PRIORITY CONSIDERATION <b>standard</b>	CLASSIFICATION OF DRUG <b>1</b>	DESIRED COMPLETION DATE <b>April 15, 2008</b>	
NAME OF FIRM: <b>Discovery</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<div> <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER </div> <div> <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> FINAL PRINTED LABELING </div> <div> <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> LABELING REVISION </div> <div> <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE </div> <div> <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> FORMULATIVE REVIEW </div> <div> <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> PAPER NDA <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): </div> <div> <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> CONTROL SUPPLEMENT </div>				
<b>II. BIOMETRICS</b>				
<div> <input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> CHEMISTRY REVIEW </div> <div> <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> PHARMACOLOGY </div> <div> <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> BIOPHARMACEUTICS </div> <div> <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): </div> <div> <input type="checkbox"/> OTHER (SPECIFY BELOW): </div>				
<b>III. BIOPHARMACEUTICS</b>				
<div> <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> DEFICIENCY LETTER RESPONSE </div> <div> <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS </div> <div> <input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST </div>				
<b>IV. DRUG SAFETY</b>				
<div> <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY </div> <div> <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE </div> <div> <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> POISON RISK ANALYSIS </div> <div> <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP </div>				
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<div> <input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL </div>				
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> Please perform DDMAC review of NDA 21-746 (resubmission) for Surfaxin (lucinactant) Intratracheal Suspension. The labeling is available in the EDR (submission date November 12, 2007). If you have any questions, please contact me at 301-796-1212. PDUFA goal: May 1, 2008.				
SIGNATURE OF REQUESTOR <b>Lori Garcia</b>			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER	

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/s/

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Lori Garcia  
2/25/2008 02:48:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="text-align: center;">REQUEST FOR CONSULTATION</h2>		
TO (Division/Office): <b>Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447</b>			FROM: Lori Garcia, R.Ph., Regulatory Project Manager Division of Pulmonary and Allergy Products	
DATE February 25, 2008	IND NO.	NDA NO. NDA 21-746	TYPE OF DOCUMENT Original NDA (resubmission)	DATE OF DOCUMENT October 31, 2007
NAME OF DRUG Surfaxin (lucinafant)	PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE April 15, 2008	
NAME OF FIRM: Discovery				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NEW PROTOCOL  <input type="checkbox"/> PROGRESS REPORT  <input type="checkbox"/> NEW CORRESPONDENCE  <input type="checkbox"/> DRUG ADVERTISING  <input type="checkbox"/> ADVERSE REACTION REPORT  <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION  <input type="checkbox"/> MEETING PLANNED BY </div> <div style="width: 33%;"> <input type="checkbox"/> PRE--NDA MEETING  <input type="checkbox"/> END OF PHASE II MEETING  <input type="checkbox"/> RESUBMISSION  <input type="checkbox"/> SAFETY/EFFICACY  <input type="checkbox"/> PAPER NDA  <input type="checkbox"/> CONTROL SUPPLEMENT </div> <div style="width: 33%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER  <input type="checkbox"/> FINAL PRINTED LABELING  <input type="checkbox"/> LABELING REVISION  <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE  <input type="checkbox"/> FORMULATIVE REVIEW  <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>Trade name review</b> </div> </div>				
<b>II. BIOMETRICS</b>				
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<b>III. BIOPHARMACEUTICS</b>				
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<b>IV. DRUG EXPERIENCE</b>				
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<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please perform DMETS review of NDA 21-746 (resubmission) for Surfaxin (lucinafant) Intratracheal Suspension. The labeling is available in the EDR under the November 12, 2007, submission. If you have any questions, please contact me at 301-796-1212.				
<b>PDUFA DATE: May 1, 2008</b> <b>ATTACHMENTS:</b> Draft Package Insert, Container and Carton Labels <b>CC:</b> Archival IND/NDA 21-746 HFD-570/Division File HFD-570/RPM HFD-570/Reviewers and Team Leaders				
NAME AND PHONE NUMBER OF REQUESTER Lori Garcia		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		



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/s/

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Lori Garcia  
2/25/2008 02:44:13 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

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

Attn: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs

Dear Ms. Hurley:

We acknowledge receipt on October 17, 2008 of your October 17, 2008 resubmission to your new drug application for Surfaxin (lucinactant) Intratracheal Suspension.

We consider this a complete, class 2 response to our May 1, 2008 action letter. Therefore, the user fee goal date is April 17, 2009.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any question, call Angela Robinson, Senior Regulatory Project Manager, at (301) 796-2284.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Sandra Barnes

11/14/2008 01:43:12 PM



NDA 21-746

**INFORMATION REQUEST LETTER**

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

Attn: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs

Dear Dr. Hurley:

Please refer to your April 13, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

We also refer to your submission dated October 31, 2007.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide an updated list of all sites involved in the manufacturing and testing of the drug product and drug substances. Specify the activities performed at each site and provide the name of the responsible party. If any given site is no longer involved in the manufacturing/testing activity, provide the date of the last involvement, and state if you would like to withdraw the site or if you wish to keep it active as an alternate manufacturing/testing site.

If you have any questions, call LCDR Lori Garcia, Senior Regulatory Management Officer, at 301-796-1212.

Sincerely,

*{See appended electronic signature page}*

Ali Al Hakim, Ph.D.  
Chief, Branch II  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Ali Al-Hakim

1/11/2008 01:26:10 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Office/Division): <b>Office of Pharmaceutical Science and New Drug Microbiology Staff</b>			FROM (Name, Office/Division, and Phone Number of Requestor): <b>Angela Robinson, OND/DPAP</b> <b>301-796-2284</b>		
DATE <b>11/05/08</b>	IND NO.	NDA NO. <b>21-746</b>	TYPE OF DOCUMENT <b>Class 2 Resubmission</b>	DATE OF DOCUMENT <b>10/17/08</b>	
NAME OF DRUG <b>Surfaxin (lucinactant)</b>		PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE <b>2/27/09</b>	
NAME OF FIRM: <b>Discovery Labs</b>					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input checked="" type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):	
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<b>III. BIOPHARMACEUTICS</b>					
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<b>IV. DRUG SAFETY</b>					
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> NONCLINICAL		
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> Please review the complete response to the micro approvability issues stated in the approvable letter dated, May 1, 2008. The pertinent review volumes were delivered 11/5/08 to Pawar.					
<b>PDUFA Goal Date:</b> April 17, 2009					
SIGNATURE OF REQUESTOR <b>Angela Robinson</b>			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

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Angela Robinson  
11/6/2008 01:47:36 PM

# MEMORANDUM OF EMAIL COMMUNICATION

DATE: December 14, 2007

APPLICATION NUMBER: NDA 21-746

BETWEEN:

Name: Marjorie Hurley  
Representing: Discovery

AND

Name: Lori Garcia, R.Ph., Regulatory Project Manager  
Division of Pulmonary and Allergy Products

SUBJECT: CMC issues

---

**From:** Hurley, Marjorie [mailto:MHurley@DiscoveryLabs.com]

**Sent:** Friday, December 14, 2007 11:16 AM

**To:** Garcia, Lori

**Subject:** cmc request, SPL

Dear Lori,

After the teleconference on December 12, we fully appreciate the short review time and the criticality of scheduling the manufacturing site inspection and review of the 12 month stability results for the new product batches. Therefore, we are re-evaluating the facility readiness schedule and resource allocation and are looking for any opportunities to accelerate our timelines. I will be providing revised dates early next week.

Discovery also plans to submit the following documents next week:

- 9 month stability data for new Surfaxin product batches (T7002, T7003, T7004) at 5°C and 15°C
- Stability data tables and graphs organized by test parameter
- Summary of any changes to the manufacturing process, equipment, SOPs, and microbiological methods

Please confirm the total number of review copies we should provide and if they should be sent to the document control room.

We also are trying to have the SPL available for submission next week. In any case, it should be available before year end.

During the teleconference, there was a question regarding the change in the filling machine. Discovery would like to clarify that the scope of this change is limited to the filling equipment only and does not include the capping equipment or capping process.

Please forward this information to attendees of the conference call if appropriate.



Best regards,

Marjorie

Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs  
Discovery Laboratories, Inc.  
2600 Kelly Road, Suite 100  
Warrington, PA 18976  
215-488-9360  
[mhurley@discoverylabs.com](mailto:mhurley@discoverylabs.com)

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/s/

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Lori Garcia  
1/18/2008 05:22:43 PM  
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO ( <i>Office/Division</i> ): OPS/NDMS, HFD-805 WO Bldg 21		FROM ( <i>Name, Office/Division, and Phone Number of Requestor</i> ): Lori Garcia, Senior Regulatory Project Manager OND/DPAP, (301) 796-1212		
DATE 12/4/07	IND NO.	NDA NO. 21-746	TYPE OF DOCUMENT resubmission	DATE OF DOCUMENT 10/31/07
NAME OF DRUG Surfaxin	PRIORITY CONSIDERATION standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 1, 2008
NAME OF FIRM: Discovery Labs				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input checked="" type="checkbox"/> RESUBMISSION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> PAPER NDA <input checked="" type="checkbox"/> OTHER ( <i>SPECIFY BELOW</i> ): <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> CONTROL SUPPLEMENT				
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<b>III. BIOPHARMACEUTICS</b>				
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<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS ( <i>List below</i> ) <input type="checkbox"/> POISON RISK ANALYSIS <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL				
<p><b>COMMENTS / SPECIAL INSTRUCTIONS:</b> Please review the complete response to the micro approvability issues stated in the approvable letter dated March 31, 2006. A copy of this consult, along with the pertinent review volumes will be delivered to you.</p> <p>PDUFA goal date: May 1, 2008.</p>				
SIGNATURE OF REQUESTOR		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

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Lori Garcia  
12/4/2007 05:40:37 PM



NDA 21-746

**INFORMATION REQUEST LETTER**

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

Attn: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs

Dear Dr. Hurley:

Please refer to your April 13, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

We also refer to your submission dated October 31, 2007.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Clarify the closure dates for your drug product manufacturing facility (Totowa, NJ) and specify the exact date when the facility will be available for inspection.
2. We note that the drug product manufacturing process and the analytical methods were significantly changed. Specify when the update on the pending stability data (i.e., 9 and 12 month data points) for the new drug product batches will be submitted to the application.
3. Provide tabular summaries of your stability data, organized by test parameter, and separated by manufacturing site, batch, storage conditions and container closure system. Provide graphical summaries of any trending stability data, organized by test parameter, including mean and individual data.

While every effort will be made to review the stability updates, their review will depend on the timeliness of submission, extent of submitted data, and available resources. Therefore, and as per Good Review Management Practice (GRMP) timelines, we may not be able to review any amendments to stability data late in the review cycle. Shelf-life will be limited to the available stability real time data submitted in the NDA.

If you have any questions, call LCDR Lori Garcia, Senior Regulatory Project Manager, at 301-796-1212.

Sincerely,

*{See appended electronic signature page}*

Ali Al Hakim, Ph.D.

Chief, Branch II

Division of Pre-Marketing Assessment I

Office of New Drug Quality Assessment

Center for Drug Evaluation and Research

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/s/

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Ali Al-Hakim

11/29/2007 10:12:04 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

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

Attn: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs

Dear Dr. Hurley:

We acknowledge receipt on November 1, 2007, of your October 31, 2007, resubmission to your new drug application for Surfaxin (lucinactant) Intratracheal Suspension.

We consider this a complete, class 2 response to our March 31, 2006, action letter. Therefore, the user fee goal date is May 1, 2008.

If you have any question, call LCDR Lori Garcia, Senior Regulatory Project Management Officer, at (301) 796-1212.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Supervisory CSO  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research



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/s/

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Lori Garcia  
11/15/2007 06:45:22 PM  
signed for Sandy Barnes



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

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

Attn: Marjorie Hurley, Pharm.D.  
Vice President, Regulatory Affairs

Dear Dr. Hurley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

We also refer to your September 10, 2007, submission, containing a request for FDA feedback on the proposed extent and format of the requested safety update report.

We have reviewed the referenced material and have the following comment.

1. Your request to submit only new safety information which has not been submitted previously is acceptable. (b) (4)

Include CRFs for those subjects in the NDA resubmission. In addition, we request that you submit safety data for all lucinactant studies ongoing at the time of the NDA resubmission.

If you have any questions, call LCDR Lori Garcia, Senior Regulatory Project Manager, at (301) 796-1212.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Badrul Chowdhury  
10/22/2007 11:57:27 AM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation  
ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 18, 2007

<b>To:</b> Margie Hurley	<b>From:</b> Ladan Jafari
<b>Company:</b> Discovery	Division of Pulmonary and Allergy Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b>
<b>Phone number:</b> 215-488-9300	<b>Phone number:</b>
<b>Subject:</b> NDA 21-746	

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**Total Number of Pages Including Cover:** 11

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**Comments:** Meeting minutes

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**Document to be mailed:** ☐ YES ☒ NO

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## MEMORANDUM OF TELECONFERENCE

DATE: October 27, 2004  
APPLICATIONS: NDA 21-704, IND 40,287  
DRUG NAME: Surfaxin (lucinactant) Intratracheal Suspension  
SPONSOR: Discovery Laboratories, Inc.

Participants: Katherine Tsokas, Director, Regulatory Affairs  
Chris Schaber, Ph.D., Exec VP, Drug Development & Regulatory Compliance  
Robert Segal, M.D., VP, Clinical Research & New Drug Evaluation  
Tony Killian, M.D., VP, Medical Monitor

Phone: 215-340-4699

FDA: Division of Pulmonary & Allergy Drug Products, HFD-570  
Harry Gunkel, M.D., Medical Reviewer  
Peter Starke, M.D., Medical Team Leader  
Sue-Jane Wang, Ph.D., Biostatistics Team Leader (Actg)  
Badrul Chowdhury, M.D., Ph.D., Director  
Christine Yu, R.Ph., Regulatory Project Manager

The Division stated that they initiated this teleconference to resolve issues arising from two submissions under IND 40,287 and NDA 21-746, both applications for Surfaxin, as well as a question from Discovery relayed by phone.

1. September 27, 2004, submission 218 to IND 40,287, a proposed Phase 3b study

In response to the Division's request for clarification, Discovery stated that it had been their original intention to submit results of the proposed 3b study during the review of NDA 21-746. The Division noted that the study could not realistically be conducted and results submitted during the review time remaining. In the unlikely event that the final study report would be submitted, it would extend the review clock. The Division asked if the protocol had been finalized. Discovery responded that the final protocol has not yet been completed; accordingly, the study has not been started. The Division stated that under those circumstances, it would be premature to discuss a study to possibly add new information to the package insert before there is a package insert. Although it is Discovery's decision, the Division recommended that the company conduct the phase 3b after the Agency has taken an action on NDA 21-746.

Discovery stated that they will wait until the Agency takes an action on the NDA before conducting the study.

2. Submission dated October 8, 2004, to NDA 21-746, Response to Request for Information.

On September 24, 2004, the Division had requested that Discovery "Submit the interim statistical analysis reports for the primary co-endpoints originally defined and at the time of changing the primary efficacy co-endpoints." In a submission dated October 8, 2004, Discovery responded that, "There were not any formal interim analyses conducted by the DSMB (Data Safety Monitoring Board)...As such, no reports of such analyses exist." However, in NDA 21-746, the study report of KL4-IRDS-06 (Module 5, volume 1.1, paragraph 11.4.2.3, page 63) contains the statement, "There were two formal interim efficacy analyses performed on the primary endpoints by the DSMB." Also, during the pre-NDA meeting for IND 40,287 on June 13, 2003, the statistical consultant for Discovery had indicated that an interim analysis had been performed. The Division requested additional clarification of these discrepancies and again requested the reports.

Discovery responded that the study had not planned for an interim analysis and that they (Discovery) did not perform one. Discovery stated, however, that the DSMB performed interim analyses as needed for their safety monitoring role, but did not unblind the data. The Division again pointed to the information in the NDA about results of interim analyses and asked Discovery to clarify this discrepancy. Discovery stated that they would look into it and follow up.

The Division further specified that they were looking for information about when the interim analyses were performed in relation to the time when the primary endpoint was changed. The Division requested minutes from all DSMB meetings. Discovery agreed to submit the minutes from the DSMB meetings.

Post-teleconference note: Discovery submitted the requested DSMB information to the NDA on November 1, 2004.

- 3.



clarification, the Division stated that the new study can be submitted to the existing IND 40,287.

The teleconference concluded at this time.

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/s/

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Christine Yu  
11/24/04 02:26:29 PM  
CSO

NDA 21-746  
Drug: Surfaxin  
Applicant: Discovery  
Meeting Date: December 21, 2006  
IMTS: 20327  
Page 1

**Discovery Representatives:**

Marjorie Hurley, Pharm.D., VP, Regulatory Affairs  
Charles Katzer, Sr. VP, Manufacturing Operations  
Gerald Orehostky, VP, Quality Operations  
Robert Segal, M.D., SR. VP, Medical & Scientific Affairs & Chief Medical Officer  
Russell Clayton, DO, VP, Worldwide Clinical Research & Development  
Margaret Filipiak, MRPharmS, Associate Director, Regulatory Affairs  
David Lopez, Executive Vice President

**Division of Pulmonary & Allergy Products (DPAP) Representatives:**

Eugenia Nashed, Ph.D., CMC Reviewer  
Prasad Peri, Ph.D., Pharmaceutical Assessment Lead  
Blair Fraser, Ph.D., Branch Chief, ONDQA  
Anthony Durmowicz, M.D., Medical Reviewer  
Sally Seymour, M.D., Medical Team Leader  
Huiqing Hao, Ph.D., Pharmacology/Toxicology Reviewer  
Timothy McGovern, Ph.D., Pharmacology/Toxicology Supervisor  
Badrul Chowdhury, M.D., Ph.D., Director  
Ladan Jafari, Regulatory Health Project Manager

**Background:** Discovery submitted a meeting request dated September 27, 2006, to discuss certain issues of the approvable letter dated March 31, 2006. This meeting request served as the meeting package, however, Discovery also submitted supporting documents dated October 9, and November 27, 2006. The meeting package and the supporting documents contained a list of questions to be discussed at this meeting. Upon review of the briefing package and the supporting documents, the Division responded to Discovery's questions via FAX on December 20, 2006. The content of that FAX is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Discovery's questions are in ***bold italics***; FDA's response is in *Italics*; discussion is in normal font.



Dr. Chowdhury initiated the meeting and stated that in order to assure a quality review of the meeting package, we expect that a complete package be submitted in one submission and not multiple submissions. Dr. Chowdhury also asked that in the future Discovery identify the type of questions and its respective disciplines so that appropriate individuals could be invited to the meeting. In addition, Dr. Chowdhury reminded Discovery that although it is our intention to send responses to sponsors questions in advance of the meeting, this procedure is at the discretion of the Division pending the issues involved. Finally, Dr. Chowdhury asked that this meeting be used to clarify any issues of the approvable letter and not as a forum to negotiate the content of the approvable letter.

1. ***Does the Agency agree with the proposal for manufacturing new process validation batches and submission of the related stability dataset to be included in the Complete Response and prior to final approval?***

***Is it acceptable to the Agency to submit additional stability data during the review cycle prior to final approval?***

**Response:**

*You may submit release and stability data from the new process validation batches as long as comparative data from other batches are presented. Note that specifications will take into account all data provided.*

*Due to the strict review time lines and workload, we strongly recommend that you provide a complete application. However, the approved shelf life will be dependent on the real time data provided.*

*Note that it is expected that both the in-vitro and bioassay studies will provide evidence of positive activity. Any substantial differences between in-vitro and bioassay activity results would be cause for concern regarding product stability/activity.*

2. ***Does the Agency agree that the data to be provided in the side-by-side comparison of "pre-change" SURFAXIN lots to "post-change" SURFAXIN as described in Attachment 2 allows the assessment of the comparability of the drug product used in pivotal clinical trials to the to be marketed drug product?***

**Response:**

*Your approach for CMC comparative data presentation seems reasonable. However, present data collected for all orientations and time points. After approval, you may request deletion of some storage orientations from the stability protocol, based on actual stability data.*

*The data found in the fetal lamb research paper (Pediatrics 2006, vol 117:295-303) provide some evidence that lots used in the clinical studies had bioactivity, however, you will still need to link the clinical lots to the current lots using a validated bioassay method, in order to assure continuity from clinical trials to the to-be-manufactured drug product.*

**Discussion:**

- Discovery asked for clarification regarding the in-vivo bioassay itself and its design.
  - The Division stated that the rabbit model should show comparable bioactivity to the lamb model since the lamb model was used to demonstrate the bioactivity of the batches used in pivotal clinical trials. The Division suggested that Discovery perform a side by side comparison of the lamb and rabbit bioassays. The lamb assay should be carried out as outlined in the article noted above and the results could be used to link the current drug batches to the clinical batches. The comparative data should be reproducible, i.e., at least three tests for each of three newly made batches should show similar results. Alternatively, Discovery could perform another clinical trial using batches tested in the rabbit bioassay.
- Discovery indicated that the comparison of the two models may not be appropriate and asked if the Division would accept a bioactivity test in the rabbit model only, using a marketed drug as a positive control.
  - The Division did not agree with Discovery's proposal and stated that while variability may be high in this type of bioassay, if the study is done properly, the results could be reproduced. The previously conducted study in the lamb model is the only link between demonstrated bioactivity in an animal model and efficacy in clinical trials. The rabbit model needs to be linked to the lamb model to support its use in verifying Surfaxin bioactivity. The Division also stated that it is critical to conduct the same methodology used in the previous lamb study but it is not necessary to include the same treatment arms, namely a positive control.
- Discovery acknowledged the Division's position and agreed to include positive controls or a reference standard in the rabbit model validation study. Discovery sought confirmation that it may be possible to eventually reduce or remove the need for the positive control, and asked if measurements at a 30 minute time point were acceptable and if the Division would provide comments on a revised study protocol.

- The Division agreed to the possible reduction or elimination of the positive control pending review of data and to the proposed 30 minute time point for measurements. The Division is amenable to providing feedback on a protocol in as timely a manner as possible.

**3. Does the Agency agree with Discovery's approach for setting release and shelf life specifications for SURFAXIN, establishing shelf-life, and for evaluating variability?**

**Response**

*Your approach of selecting batches seems reasonable. Establishing shelf life and assessing variability in the batches provided are review issues.*

**4. Does the Agency agree with Discovery's proposal for reporting, identifying and qualifying impurities in the active drug substances and SURFAXIN drug product?**

**Response:**

*Your approach is reasonable for the drug substance sinapultide.*

*For the other three actives (lipids) ICH Q3A(R) should apply, but this will be a review issue.*

*For the drug product, the qualification limits should be based on preclinical evaluation of the reported impurities and their evaluation of the complete data set presented in the meeting package and the NDA.*

**5. Does the Agency agree with Discovery's approach described in Attachment 5 for characterizing (b) (4) and evaluating the effect of these (b) (4) on SURFAXIN drug product activity?**

**Response:**

*Your approach to characterization of the (b) (4) and changes occurring with time in the physicochemical characterization of drug product seem reasonable.*

*Your proposal to evaluate the effect of the (b) (4) on drug product activity in vitro using PBS and in vivo using the fetal rabbit bioassay is acceptable, although it is noted that this type of evaluation was not requested in the referenced Item 20 of the March 31, 2006 Approvable Letter. Item 20 referred to Item 2 of the same letter which addresses the safety qualification of drug substance and drug related impurities.*

**6. Does the Agency believe that Discovery has adequately addressed the following:**

- 1. Justification of the proposed  $\geq 50\%$  increase in compliance over control using this assay to establish "pass/fail" criteria for SURFAXIN lots over time,**
- 2. Issues regarding the inclusion of a reference standard in the testing for drug product using the fetal rabbit bioactivity,**
- 3. Issue of the perceived inflation of the overall type I error and explained how the type I error is controlled by the approach described in the response to Item 12e from the February 11, 2005 Approvable Letter?**

**Response:**

*You have not adequately addressed the proposed positive criterion of  $\geq 50\%$  increase in compliance over control. The submitted research paper on the fetal lamb model does provide information that may be supportive of a criterion of  $\geq 150\%$  increase (2.5-fold) in compliance. There is currently no evidence to indicate that a 50% increase in the animal bioassay will translate to a clinically efficacious effect.*

*You have not adequately addressed the issue regarding the inclusion of a reference standard. Include a reference standard in your testing for drug product bioactivity and justify the appropriateness of your selection. Once sufficient data are generated to assure the validity and reproducibility of the assay under the testing conditions, this requirement may be reduced or waived.*

*You have adequately addressed the issue regarding the inflation and control of the overall type I error.*

7. ***Does the Agency agree with the above approach to providing an update of Module 3 in its entirety with the Complete Response?***

**Response:**

*You may submit an updated Module 3 highlighting the changes from the previous version.*

8. ***Does the Agency agree that (b) (4) has addressed the Agency's concerns and that the appropriate controls are in place to ensure the acceptability of (b) (4) as a starting material? Is it acceptable to the Agency that (b) (4) supplied by (b) (4) be used in the manufacture of SURFAXIN?***

**Response:**

*The acceptability of (b) (4) as a supplier of (b) (4) will have to await the review of (b) (4) amendment in response to our March 29, 2006, deficiency letter. This DMF will be reviewed when we receive the complete response to the action letter.*

**Discussion:**

- Discovery asked if (b) (4) is acceptable as a starting material. Discovery indicated that the two suppliers of (b) (4) are not regulated by the FDA, however, are willing to share their information with the Agency.
  - The Division reminded Discovery that until the complete response to the NDA is submitted, the DMF would not be reviewed. However, the response seems reasonable. The Division stated that the DMF holder should pay special attention to the impurity profile for (b) (4)

***Question from Nov. 16, 2006, amendment***

***Does the Agency agree with the Discovery's approach for qualifying the safety of SURFAXIN impurities?***

**Response:**

*In general, your proposed approach for qualifying the safety of SURFAXIN impurities through a ferret study employing two intratracheal bolus doses of degraded SURFAXIN is acceptable. It is not clear from the background package what daily dose of each impurity will be administered to the ferrets. We note that your submission refers to an expected safety factor of (b) (4). The administered daily dose of each impurity (usually in mg/kg body weight or mg/g lung tissues units) should provide at least a 10-fold safety margin in comparison to the maximum expected daily human dose based on the specification set for each impurity.*

*Provide justification from the literature to support the qualification of any lipid-related impurities that are not qualified by the proposed study and your contention that they are typical breakdown products of mammalian lung surfactant and are found in many exogenous surfactants.*

**Discussion:**

Discovery indicated that testing Surfaxin and related impurities are limited by a potential for animal drowning due to the physical nature of the test substances. Discovery raised concerns that they may not achieve the 10-fold safety margin in the impurity qualification study.

- The Division stated that the purpose of the study is to evaluate toxicities of the impurities at doses that are sufficiently higher than expected human exposure and to identify a no-adverse-effect level (NOAEL). The animal NOAELs for the impurities should provide adequate safety margins for potential human exposures. Discovery should consider increasing the impurity concentration in the administered product or increase the number of daily administrations if possible. As impurities provide no therapeutic benefit, it is difficult to support reducing the expectations regarding safety margins. The Division stated that Discovery could justify the maximum feasible dose for the toxicology study and lower the impurity specifications if achieved safety margins are not acceptable.
- Discovery asked about the dosing of the animals in a 24-hour period and asked if they could extend it to 48 hours instead in order to increase the total dose.
- The Division stated that ideally the dosing regimen in the toxicology study should be parallel that in the clinical program. However, pending any technical limitations, dosing within 48 hours may be acceptable.

- Discovery asked if they could use tris-buffer for a vehicle control.
  - The Division stated that it is reasonable. However, if too much negative control is instilled in the lung, injury such as ARDS may develop. The Division suggested that an active control, such as a fresh drug batch, also be used. The Division also suggested that Discovery look for any reversibility at 14-days and include an untreated control arm since there is limited experience with ferrets as a test species.
- Discovery asked if they could share the proposal for their impurity qualification study and ask for feedback from the Division.
  - The Division stated that we could review the proposal for this study but any data would be reviewed when the complete response to the approvable letter is submitted.

***Question from Nov. 27, 2006, amendment***

***Does the Agency agree that the process improvements described above, together with a full characterization profile, will increase process control and improve product quality while maintaining comparability of SURFAXIN clinical batches with the to-be-marketed SURFAXIN batches?***

**Response:**

*Your approach is reasonable but this is a review issue and will be dependent on the data presented for the optimized process.*

***Request from Nov. 27, 2006, amendment***

***Discovery respectfully requests feedback from the Agency regarding (1) the genesis of the recommended criterion for positive Surfaxin bioactivity of  $\geq 200\%$  (3-fold) increase of compliance over control, and (2) the envisioned utility of the positive control in the bioassay.***

**Response:**

*We recommended a criterion for positive Surfaxin bioactivity of  $\geq 200\%$  based on experience with previous surfactant products in showing positive bioactivity. We recognize that this criterion may vary depending on the given test methodologies and models used and, therefore, allowed for the submission of a justification for alternate criterion to be applied. We recommend the inclusion of a positive control or internal reference to demonstrate that a given assay under the test methodologies produces expected results for either a previously marketed product or other relevant standard. As noted in our response to Question 6, this requirement may be reduced or waived once sufficient data are generated to assure the validity and reproducibility of the assay under the testing conditions.*

**Additional item for discussion:**

- The Division referred Discovery to page 33 of the briefing package dated September 27, 2006, and asked that Discovery check to see if this type of agglomerates appear all the time or just on this particular lot. This is considered as an important parameter to monitor for the drug product.
  - Discovery agreed and stated that they would test for this as well.



NDA 21-746  
Drug: Surfaxin  
Applicant: Discovery  
Meeting Date: December 21, 2006  
IMTS: 20327  
Page 10

Drafted by: LJ/1-5-06

Initialed by: Nashed/1-9-07  
Peri/1-9-07  
Fraser/1-9-07  
Hao/1-12-07  
McGovern/1-12-07  
Durmowicz/1-8-07  
Seymour/1-8-07  
Chowdhury/1-17-07

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Ladan Jafari

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

mtg DN

Discovery Laboratories, Inc.  
2600 Kelly Road  
Warrington, PA 18976

Attention: Katherine A. Tsokas, J.D.  
Director, Regulatory Affairs

Dear Ms. Tsokas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for Surfaxin (lucinactant) Intratracheal Suspension for use in neonatal respiratory distress syndrome (RDS).

We also refer to your November 23, 2005, correspondence, received November 25, 2005, requesting a meeting to gain agreement with the agency regarding the appropriateness of data submitted in relation to drug product impurity qualification and analytical methodology and confirm that there are no additional issues with the pending NDA. We have considered your request and concluded that the meeting at this time would not be productive. The questions you would like to discuss are issues requiring a complete review of your October 5, 2005, resubmission.

If you have any questions, call me at 301-796-1316.

Sincerely,

*{See appended electronic signature page}*

Christine Yu, R.Ph.  
Sr. Regulatory Management Officer  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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Christine Yu  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): <b>Huiqing Hao, Ph.D., Timothy McGovern, Ph.D.</b> <b>Pharmacology Review team</b>			FROM: <b>Christine Yu, R.Ph.</b> <b>Regulatory Project Manager</b>	
DATE <b>November 22, 2005</b>	IND NO.	NDA NO. <b>21-746</b>	TYPE OF DOCUMENT <b>NDA resubmission</b>	DATE OF DOCUMENT <b>October 5, 2005</b>
NAME OF DRUG <b>Surfaxin (lucinactant)</b> <b>Intratracheal Suspension</b>		PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>1</b>	DESIRED COMPLETION DATE <b>January 23, 2006</b>
NAME OF FIRM: <b>Discovery Laboratories, Inc.</b>				
REASON FOR REQUEST				
I. GENERAL				
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V. SCIENTIFIC INVESTIGATIONS				
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COMMENTS/SPECIAL INSTRUCTIONS: Please provide a pharmacology review of applicant's response to question 1a and 11b, about qualification of impurities at or above 0.15%. Please refer to specifications for drug product components and maximum impurities levels located in Vol. 1, pp. 8-11, and pp. 72-75, and supporting documentation in Appendix 11-13, of the Oct 5 <sup>th</sup> , 2005 submission.				
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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 22, 2005

<b>To:</b> Katherine Tsokas, J.D. Director, Regulatory Affairs	<b>From:</b> Christine Yu, R.Ph. Regulatory Project Manager
<b>Company:</b> Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 215-488-9350	<b>Phone number:</b> 301-796-1316
<b>Subject:</b> NDA 21-746 Surfaxin Clinical Information Request	
<b>Total no. of pages including cover:</b> 2	

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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We refer to your NDA 21-746 for Surfaxin (lucinactant) Intratracheal Suspension and have the following request.

We note that the complete response includes amended final study reports for studies KL4-IRDS-06 and KL4-IRDS-02, as well as the Integrated Summary of Efficacy; however, the amended portions have not been specified. To facilitate review of the application, provide annotated amended final study reports to note the portions that have been amended from the previous final reports. Alternatively, provide a written guide to the documents detailing where they have been amended and how.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu @ 301-796-1316.



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Christine Yu  
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CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): <b>Division of Drug Marketing, Advertising and Communications, HFD-42, PKLN Room 17b-17</b>		FROM: Christine Yu, R.Ph. Division of Pulmonary & Allergy Drug Products, HFD-570		
DATE October 31, 2005	IND NO.	NDA NO. 21-369	TYPE OF DOCUMENT NDA resubmission	DATE OF DOCUMENT October 5, 2005
NAME OF DRUG Surfaxin (lucinactant) Intratracheal Suspension		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE February 13, 2006
NAME OF FIRM: Discovery Laboratories, Inc.				
REASON FOR REQUEST				
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V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: <b>Please perform DDMAC review of the October 5, 2005 resubmission to NDA 21-746. Volume 1 of the resubmission is included with the paper copy of the consult. Please contact me if you have any questions at 301-796-1316.</b>				
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Christine Yu  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34</b>			FROM: Christine Yu, R.Ph. Regulatory Project Manager, HFD-570	
DATE 31 October 2005	IND NO.	NDA NO. 21-746	TYPE OF DOCUMENT NDA Resubmission	DATE OF DOCUMENT October 5, 2005
NAME OF DRUG Surfaxin (lucinaftant) Intratracheal Suspension		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE February 13, 2006
NAME OF FIRM: Discovery Laboratories, Inc.				
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<b>V. SCIENTIFIC INVESTIGATIONS</b>				
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<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Please perform labeling and trade name review for resubmission to NDA 21-746. Copy of Volume 1 of the resubmission is attached with the paper copy of the consult. Wrap meeting for this application is planned for the week of February 23, 2005. Please contact me if you have any questions, 301-796-1316.				
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11/2/2005 05:48:32 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<b>REQUEST FOR CONSULTATION</b>	
TO (Division/Office): <b>David Hussong, Ph.D.</b> <b>Microbiology, HFD-805</b>			FROM: <b>Christine Yu, R.Ph.</b> <b>Regulatory Project Manager, HFD-570</b>	
DATE <b>October 31, 2005</b>	IND NO.	NDA NO. <b>21-746</b>	TYPE OF DOCUMENT <b>NDA Resubmission</b>	DATE OF DOCUMENT <b>October 5, 2005</b>
NAME OF DRUG <b>Survanta (beractant)</b> <b>Intratracheal suspension</b>		PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>Type 1</b>	DESIRED COMPLETION DATE <b><i>February 13, 2006</i></b>
NAME OF FIRM: <b>Discovery Laboratories, Inc.</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input checked="" type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Please perform microbiology review of the October 5, 2005, NDA 21-746 resubmission, as well as associated and applicable DMFs. Copy of the resubmission has been delivered to your office. If you have any questions, please contact me at 796-1316.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

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Christine Yu  
11/2/2005 05:20:46 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

Discovery Laboratories, Inc.  
2600 Kelly Road  
Warrington, PA 18976

Attention: Katherine A. Tsokas, J.D.  
Director, Regulatory Affairs

Dear Ms. Tsokas:

We acknowledge receipt on October 6, 2005, of your October 5, 2005, resubmission to your new drug application for Surfaxin (lucinactant) Intratracheal Suspension for use in neonatal respiratory distress syndrome (RDS).

We consider this a complete, class 2 response to our February 11, 2005, action letter. Therefore, the user fee goal date is April 6, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver granted on May 17, 2004, for the pediatric study requirement outside of the neonatal population for this application.

If you have any question, call Christine Yu, R.Ph., Regulatory Project Manager, at 301-796-1316.

Sincerely,

*{See appended electronic signature page}*

Sandy Barnes  
Chief, Project Management Staff  
Division of Pulmonary and Allergy Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research



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/s/

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Christine Yu  
10/20/2005 05:00:12 PM  
Signing for Sandy Barnes, CPMS



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 16, 2005

<b>To:</b> Katherine Tsokas, J.D. Director, Regulatory Affairs	<b>From:</b> Christine Yu, R.Ph. Regulatory Project Manager
<b>Sponsor:</b> Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-488-9350	<b>Phone number:</b> 301-827-1051

**Subject:** NDA 21-746 Surfaxin (lucinaftant)  
Submission dated July 29, 2005

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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We acknowledge receipt of your submission to NDA 21-746 for Surfaxin (lucinactant) dated and received July 29, 2005.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

Comment 1

We requested that you submit “revised acceptance criteria for verification testing of incoming drug substance components.” In order for you to have methods in place to perform verification testing for the incoming drug substance components, the methods transfer for each of these components to your site must be complete. The transfer can be confirmed by providing comparative data on the same drug substance lots tested by both the suppliers and your laboratory.

Comments 1.a

We requested that you qualify individual impurities in the four drug substance components that are at or above 0.15% (relative to the drug substance components themselves). Your response states that this is currently being accomplished. When the qualification data are available for review by our pharmacology/toxicology team, submit them with your complete response.

Comment 3

DMF (b) (4) amendment dated July 29, 2005, is not a complete response to our February 11, 2005, deficiency letter.

The holder of DMF (b) (4) has not submitted a response to the deficiency letter from the Agency dated February 11, 2005.

Comment 4

We asked you to provide detailed information and comparative characterization of the old versus the new container closure system. Neither detailed or comparative information has been provided in your response to allow us to see what has changed and to assess the change in terms of the impact on the drug product (stability, formulation compatibility, etc.).

Comment 5.b

We specifically asked that you provide information about the level of (b) (4) used for the (b) (4) of the rubber stoppers. This information was not provided in the response.

Comment 7.e

We asked you to provide the investigative report that describes the source of the *Bacillus thuringiensis* contamination that was found in media fill batch FIL020B03. In response, you only provided an executive summary of the report which does not contain any of the attachments that are said to accompany the report. Our microbiological staff will need to review the actual report with attachments, not just the executive summary.

Comment 10, 14 and 18

We asked you to submit and analyze release and available stability data for drug product batches (plural) manufactured with a validated manufacturing process and filled to the container closure that is intended for marketing. You have only provided the release data for the first of three process validation batches and that the release data for the other two “will be provided as available.”

Comments 11.b

We asked that you qualify individual drug product impurities that are at or above 0.15% (relative to the drug substance components themselves). You have stated in your response that you are “in the process of qualifying these degradants at worst-case levels.” When the qualification data are available for review by our pharmacology/toxicology team, submit them with your complete response.

Comment 16

We asked that you provide data to confirm the results on the certificates of analysis (CoA) for the incoming container closure components to be used for the drug product. You have stated in your response that you “are in the process of obtaining data to confirm the results from the vendor certificates of analysis.” When you have methods in place for confirmation of the test results as well as results for comparison to CoAs, submit these with your complete response.

Comment 33

We asked that you provide detailed instructions for the labeling regarding the preparation of the drug product for administration. We also asked that you provide supportive stability data with regard to temperature, storage time, and the method of warming. Although the updated instructions are provided, there were no supporting stability data included in your partial response.

Comment 35

We asked that you include space on the label of the drug product to record the time and date when the drug is removed from the refrigerator. You did not indicate in your response whether this has been done.

Additional comments may be provided in the future.

If you have any question, call Christine Yu, Regulatory Project Manager, at (301) 827-1051.

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/s/

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Christine Yu  
8/16/2005 05:16:42 PM  
CSO

6/17/05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

Discovery Laboratories, Inc.  
2600 Kelly Road  
Warrington, PA 18976

Attention: Katherine A. Tsokas, J.D.  
Director, Regulatory Affairs

Dear Ms. Tsokas:

Please refer to your NDA 21-746 for Surfaxin (lucinactant) Intratracheal Suspension submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for use in neonatal respiratory distress syndrome (RDS).

We also refer to your June 8, 2005, correspondence, received June 9, 2005, requesting a meeting to clarify comments from the action letter dated February 11, 2005.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The teleconference is scheduled for:

Date: Friday, July 29, 2005  
Time: 11:00 AM - 12:00 PM  
Phone Arrangements: To be determined

CDER participants: Division of Pulmonary & Allergy Drug Products (tentative list)

Eugenia Nashed, Ph.D., Chemistry, Manufacturing & Control (CMC) Reviewer  
Suong Tran, Ph.D., CMC Review  
Rik Lostritto, Ph.D., CMC Team Leader  
Huiqing Hao, Ph.D., Pharmacologist  
Joseph Sun, Ph.D., Supervisory Pharmacologist  
Harry Gunkel, M.D., Medical Reviewer  
Peter Starke, M.D., Medical Team Leader  
Badrul Chowdhury, M.D., Ph.D., Director  
Christine Yu, R.Ph., Regulatory Project Manager

Provide 12 desk copies of the briefing package at least one month prior to the teleconference. If we do not receive the packages by June 29, 2005, we may cancel or reschedule the meeting.

NDA 21-746  
Teleconference confirmation  
Page 2

If you have any questions, please call me at (301) 827-1051.

Sincerely,

*{See appended electronic signature page}*

Christine Yu, R.Ph.  
Sr. Regulatory Management Officer  
Division of Pulmonary & Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Christine Yu  
6/17/05 03:26:12 PM





Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 11, 2005

<b>To:</b> Katherine Tsokas, J.D. Director, Regulatory Affairs	<b>From:</b> Christine Yu, R.Ph. Regulatory Project Manager
<b>Company:</b> Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-488-9350	<b>Phone number:</b> 301-827-1051

**Subject:** NDA 21-746 Surfaxin  
Response to submission dated April 8, 2005

**Total no. of pages including cover:** 2

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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We refer to your NDA 21-746 for Surfaxin (lucinactant) Intratracheal Suspension and to your submission dated April 8, 2005, and have the following comment.

Your proposed safety update submission, as described in items 1 through 4 of the submission, is acceptable to the Division. However, it is not acceptable to exclude all case report forms. Although it is not necessary to re-submit case report forms which were previously submitted to the NDA, include all those from studies KL4-IRDS-06 and KL4-IRDS-02 which have not been previously submitted. In addition, provide a tabular listing of all case report forms submitted to this NDA at any time and indicate the location (submission date, volume of submission, page number).

If you have any questions regarding this facsimile correspondence, please contact Christine Yu @ 301-827-1051.

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/s/

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Christine Yu  
5/11/05 01:28:59 PM  
CSO

## **Memorandum of Telephone Facsimile Correspondence**

Date: January 14, 2005

To: Katherine Tsokas, J.D.  
Director, Regulatory Affairs

Fax: 215-488-9512

From: Christine Yu, R.Ph.  
Regulatory Project Manager

Subject: NDA 21-746 Surfaxin (lucinactant) Intratracheal Suspension  
Minutes of January 10, 2005, teleconference

Reference is made to the meeting/teleconference held between representatives of you and this Division on January 10, 2005. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

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Thank you.

## MEMORANDUM OF TELECONFERENCE

DATE: January 10, 2005  
APPLICATION: NDA 21-746  
DRUG NAME: Surfaxin (lucinactant) Intratracheal Suspension  
SPONSOR: Discovery Laboratories, Inc.

Participants: Katherine Tsokas, J.D., Director, Regulatory Affairs  
Robert Segal, M.D., VP, Clinical Research & New Drug Evaluation  
Adam Ramage, Associate Director, Global Project Management  
Tim Gregory, M.D., Sr. Director, Clinical Development & Administration

FDA: Division of Pulmonary & Allergy Drug Products, HFD-570  
J Harry Gunkel, M.D., Medical Reviewer  
Christine Yu, R.Ph., Regulatory Project Manager

In a facsimile correspondence dated January 6, 2005, the Division requested two clarifications regarding results from clinical studies. The Division's questions, noted in *Italics font*, are followed by Discovery's responses and discussions at the teleconference (normal font).

1. *In the 4-month safety update (dated September 30, 2004), results of the 12-month follow-up neurologic exams are shown in RDS Table 31 of the Integrated Safety Summary, volume 28, pp 169-170. The incidences of all the abnormal neurologic findings in study KL4-IRDS-06 are >50% in all treatment groups. In contrast, the incidences in study KL4-IRDS-02 are 10-20%. The results are final for study KL4-IRDS-02, but follow-up evaluations are still ongoing in KL4-IRDS-06.*

*Provide an explanation of the large difference between the two studies.*

Dr. Gregory stated that neurological assessments were not required in the original protocol for KL4-IRDS-06 but were added later in a protocol amendment. Consequently, there were patients enrolled in the study and evaluated at 12 months without the neurological assessments. For the neonates who were not neurologically assessed, the worst case scenario was assumed, in keeping the statistical and analytical plan. Additionally, imputations of worst outcomes were also made for patients who died or were lost to follow-up. The percent lost to follow-up so far is about 3-4% for both trials. Furthermore, 12-month follow-up data are still outstanding for about 300-400 patients. (Discovery expects the assessments to be completed within a week or two.) With these various factors, the incidence of abnormal neurologic findings in KL4-IRDS-06 appears to be falsely elevated in comparison to KL4-IRDS-02. Discovery stated that an unaudited analysis indicates that the rate of abnormal neurologic findings (unimputed) appears to be about 7-13% in all three treatment groups.

Dr. Gunkel requested that the preliminary analysis results be submitted to the NDA and suggested that the final study report (FSR) for KL4-IRDS-06 present data in both ways, with and without imputation.

Discovery responded that they would submit the preliminary unaudited results to the NDA by the close of business this day, and submit the FSR data in both formats, as requested.

2. *It appears from the protocols and study reports for KL4-IRDS-06 and KL4-IRDS-02 that cranial ultrasounds were not required for the diagnosis of IVH, but the results were reported if the ultrasounds were performed. State whether ultrasounds were required for the studies. If they were required, provide the time(s) at which they were to be obtained, or provide the reference to that information in the NDA.*

Dr. Gregory stated that all neonates were required to have the ultrasounds performed. He stated that the protocol did not state so because all study centers had care protocols that required ultrasounds. The time frame for performing the ultrasounds depended on the institutional protocol, but the average was about 6 days after birth. Dr. Gregory pointed out that the patients who did not have ultrasounds for any reason are included in the "missing" category in the tables provided in the NDA.

The Division thanked Discovery for providing the clarifications, and the teleconference concluded at this time.

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/s/

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Christine Yu  
1/14/05 09:47:40 AM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 6, 2005

<b>To:</b> Katherine Tsokas, J.D. Director, Regulatory Affairs	<b>From:</b> Christine Yu, R.Ph. Regulatory Project Manager
<b>Company:</b> Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
<b>Fax number:</b> 215-488-9512	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-488-9350	<b>Phone number:</b> 301-827-1051

**Subject:** NDA 21-746 Surfaxin  
Clinical Information Request

**Total no. of pages including cover:** 2

**Comments:** \*\*\* *We will call you for the clarifications requested in this fax.* \*\*\*

**Document to be mailed:** ☐ YES ☒ NO

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We refer to your NDA 21-746 for Surfaxin (lucinactant) Intratracheal Suspension and have the following requests.

1. In the 4-month safety update (dated September 30, 2004), results of the 12-month follow-up neurologic exams are shown in RDS Table 31 of the Integrated Safety Summary, volume 28, pp 169-170. The incidences of all the abnormal neurologic findings in study KL4-IRDS-06 are >50% in all treatment groups. In contrast, the incidences in study KL4-IRDS-02 are 10-20%. The results are final for study KL4-IRDS-02, but follow-up evaluations are still ongoing in KL4-IRDS-06.

Provide an explanation of the large difference between the two studies.

2. It appears from the protocols and study reports for KL4-IRDS-06 and KL4-IRDS-02 that cranial ultrasounds were not required for the diagnosis of IVH, but the results were reported if the ultrasounds were performed. State whether ultrasounds were required for the studies. If they were required, provide the time(s) at which they were to be obtained, or provide the reference to that information in the NDA.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu @ 301-827-1051.

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/s/

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Christine Yu  
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Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** December 28, 2004

**To:** Katherine Tsokas  
Director, Regulatory Affairs

**Company:** Discovery Laboratories, Inc.

**Fax number:** 215-488-9512

**Phone number:** 215-488-9350

**From:** Christine Yu, R.Ph.  
Regulatory Project Manager

Division of Pulmonary & Allergy Drug  
Products

**Fax number:** 301-827-1271

**Phone number:** 301-827-1051

**Subject:** IND 40,287 Surfaxin in MAS  
Clinical Information Request

**Total no. of pages including cover:** 2

**Comments:**

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**Document to be mailed:**

☐ YES

☒ NO

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We refer to IND 40,287 and to your protocol KL4-MAS-03 entitled, "A multicenter, randomized, controlled trial comparing the safety and effectiveness of bronchoalveolar lavage with Surfaxin to standard care for the treatment of the meconium aspiration syndrome (MAS) in newborn infants." You notified us in your November 4, 2004, submission that enrollment in the KL4-MAS-03 study would be terminated because of slow enrollment. We also note that 69 patients were enrolled in the study. This would comprise 14 more patients than the 55 patients for whom data were submitted to NDA 21-746. Provide the following information.

1. Any deaths that occurred in the study, including patient identifier, treatment group, cause of death, and study day of death.
2. Adverse events reported for the 14 patients who were not included in the summary of the study submitted in the NDA. Provide the patient identifier, treatment group, MedDRA system organ class and preferred term, and whether the event was serious.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu @ 301-827-1051.

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/s/

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Christine Yu  
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CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** December 14, 2004

<b>To:</b> Katherine Tsokas Director, Regulatory Affairs	<b>From:</b> Christine Yu, R.Ph. Regulatory Project Manager
<b>Company:</b> Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
<b>Fax number:</b> 215-488-9301	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-488-9350	<b>Phone number:</b> 301-827-1051

**Subject:** NDA 21-746 Surfaxin  
Request for clarification

**Total no. of pages including cover:** 2

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**Comments:** \* *Please submit a response no later than Friday, December 17, 2004* \*

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**Document to be mailed:** ☐ YES ☒ NO

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We refer to your NDA 21-746 for Surfaxin (lucinactant) Intratracheal Suspension and have the following request for clarification of the data provided in your submission dated December 1, 2004, regarding how members of the Adjudication Committee determined the cause of death in KL4-IRDS-06.

1. In the patients identified by the numbers listed below, two members of the Committee appear to have agreed about RDS-related mortality, but the data provided indicates that a Committee vote also occurred for the patients. Provide explanations for why a Committee vote was taken for the following patients:

51007  
322001  
322008  
513002  
661002  
751012  
752015  
812007

2. The following patients have two contradictory votes listed from the same adjudicator. Explain and clarify these occurrences.

22002  
172001  
173015  
312009  
631008  
721001  
751019  
752042  
753025

We request that the information be submitted no later than Friday, December 17, 2004.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu @ 301-827-1051.

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/s/

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Christine Yu  
12/14/04 02:06:49 PM  
CSO



## **Memorandum of Telephone Facsimile Correspondence**

Date: November 24, 2004

To: Katherine Tsokas  
Director, Regulatory Affairs

Fax: 215-340-3940

From: Christine Yu, R.Ph.  
Regulatory Project Manager

Subject: NDA 21-746 and IND 40,287  
Surfaxin (lucinactant) Intratracheal Suspension  
Minutes of October 27, 2004, teleconference

Reference is made to the meeting/teleconference held between representatives of you and this Division on October 27, 2004. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

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Thank you.

## MEMORANDUM OF TELECONFERENCE

DATE: October 27, 2004  
APPLICATIONS: NDA 21-704, IND 40,287  
DRUG NAME: Surfaxin (lucinactant) Intratracheal Suspension  
SPONSOR: Discovery Laboratories, Inc.

Participants: Katherine Tsokas, Director, Regulatory Affairs  
Chris Schaber, Ph.D., Exec VP, Drug Development & Regulatory Compliance  
Robert Segal, M.D., VP, Clinical Research & New Drug Evaluation  
Tony Killian, M.D., VP, Medical Monitor

Phone: 215-340-4699

FDA: Division of Pulmonary & Allergy Drug Products, HFD-570  
  
Harry Gunkel, M.D., Medical Reviewer  
Peter Starke, M.D., Medical Team Leader  
Sue-Jane Wang, Ph.D., Biostatistics Team Leader (Actg)  
Badrul Chowdhury, M.D., Ph.D., Director  
Christine Yu, R.Ph., Regulatory Project Manager

The Division stated that they initiated this teleconference to resolve issues arising from two submissions under IND 40,287 and NDA 21-746, both applications for Surfaxin, as well as a question from Discovery relayed by phone.

1. September 27, 2004, submission 218 to IND 40,287, a proposed Phase 3b study

In response to the Division's request for clarification, Discovery stated that it had been their original intention to submit results of the proposed 3b study during the review of NDA 21-746. The Division noted that the study could not realistically be conducted and results submitted during the review time remaining. In the unlikely event that the final study report would be submitted, it would extend the review clock. The Division asked if the protocol had been finalized. Discovery responded that the final protocol has not yet been completed; accordingly, the study has not been started. The Division stated that under those circumstances, it would be premature to discuss a study to possibly add new information to the package insert before there is a package insert. Although it is Discovery's decision, the Division recommended that the company conduct the phase 3b after the Agency has taken an action on NDA 21-746.

Discovery stated that they will wait until the Agency takes an action on the NDA before conducting the study.

2. Submission dated October 8, 2004, to NDA 21-746, Response to Request for Information.

On September 24, 2004, the Division had requested that Discovery "Submit the interim statistical analysis reports for the primary co-endpoints originally defined and at the time of changing the primary efficacy co-endpoints." In a submission dated October 8, 2004, Discovery responded that, "There were not any formal interim analyses conducted by the DSMB (Data Safety Monitoring Board)...As such, no reports of such analyses exist." However, in NDA 21-746, the study report of KL4-IRDS-06 (Module 5, volume 1.1, paragraph 11.4.2.3, page 63) contains the statement, "There were two formal interim efficacy analyses performed on the primary endpoints by the DSMB." Also, during the pre-NDA meeting for IND 40,287 on June 13, 2003, the statistical consultant for Discovery had indicated that an interim analysis had been performed. The Division requested additional clarification of these discrepancies and again requested the reports.

Discovery responded that the study had not planned for an interim analysis and that they (Discovery) did not perform one. Discovery stated, however, that the DSMB performed interim analyses as needed for their safety monitoring role, but did not unblind the data. The Division again pointed to the information in the NDA about results of interim analyses and asked Discovery to clarify this discrepancy. Discovery stated that they would look into it and follow up.

The Division further specified that they were looking for information about when the interim analyses were performed in relation to the time when the primary endpoint was changed. The Division requested minutes from all DSMB meetings. Discovery agreed to submit the minutes from the DSMB meetings.

Post-teleconference note: Discovery submitted the requested DSMB information to the NDA on November 1, 2004.

3.  (b) (4)  


The teleconference concluded at this time.

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/s/

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Christine Yu  
11/24/04 02:26:29 PM  
CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 22, 2004

<b>To:</b> Katherine Tsokas Director, Regulatory Affairs	<b>From:</b> Christine Yu, R.Ph. Regulatory Project Manager
<b>Company:</b> Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
<b>Fax number:</b> 215-340-3940	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-340-4699 x229	<b>Phone number:</b> 301-827-1051
<b>Subject:</b> NDA 21-746 Surfaxin Request for information	
<b>Total no. of pages including cover:</b> 3	

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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We refer to your NDA 21-746 for Surfaxin and request the information specified below.

Provide the following information about all the patients who died by 14 days of age in study KL4-IRDS-06. For each patient, indicate the determination made about whether the death was RDS-related (Yes/No) for each Adjudication Committee member who reviewed the patient's death. Display the results in tabular form similar to the attached example Table. Submit the Table along with a corresponding SAS transport data file. If the Y/N response is generated from other data field(s), also include those variables in the transport data file.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu @ 301-827-1051.

[illegible]

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/s/

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Christine Yu  
11/22/04 05:25:10 PM  
CSO



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): Huiqing Hao, Ph.D., Joseph Sun, Ph.D. Pharmacology Review team, HFD-570			FROM: Christine Yu, R.Ph. Regulatory Project Manager, HFD-570	
DATE 19 November 2004	IND NO.	NDA NO. 21-746	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 19 October 2004
NAME OF DRUG Surfaxin (lucinactant) Intratracheal Suspension		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE 17 December 2004
NAME OF FIRM: Discovery Laboratories, Inc.				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> MEETING PLANNED BY				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Based on rabbit physiology, perform evaluation of the appropriateness of the proposed in vivo (biological) testing method on premature rabbits (for the purpose of establishing CMC specifications based on submitted data). The response to this consult is being requested within 30-days given PDUFA timelines. The archival copy of October 19, 2004, submission is being provided with the consult. If additional information is needed from the applicant, please let me know as soon as possible.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

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Christine Yu  
11/19/04 11:27:08 AM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 2, 2004

**To:** Katherine Tsokas  
Director, Regulatory Affairs

**Company:** Discovery Laboratories, Inc.

**Fax number:** 215-340-3940

**Phone number:** 215-340-4699 x229

**From:** Christine Yu, R.Ph.  
Regulatory Project Manager

Division of Pulmonary & Allergy Drug  
Products

**Fax number:** 301-827-1271

**Phone number:** 301-827-1051

**Subject:** NDA 21-746 Surfaxin  
Request for information

**Total no. of pages including cover:** 2

**Comments:**

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**Document to be mailed:**

☐ YES

☒ NO

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We refer to your NDA 21-746 for Surfaxin and request the information specified below. If the requested information has already been submitted in the NDA, please provide its specific location by volume and page number.

1. Provide summary information about the results of study KL4-ARDS-01. The study synopsis is included in the NDA (Module 2, vol 1.49, p 16476), but the study report is not provided. From the information submitted, it appears that the study was terminated after only 2 of the planned 36 patients were enrolled. Explain why the study was terminated early.
2. Provide additional information explaining why study KL4-ARDS-03 was terminated after only 14 of the planned 540 patients were enrolled.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu @ 301-827-1051.

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/s/

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Christine Yu  
11/2/04 04:10:59 PM  
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="text-align: center;">REQUEST FOR CONSULTATION</h2>		
TO (Division/Office): <b>Division of Drug Marketing, Advertising and Communication, HFD-42, PKLN Room 17b-17</b>		FROM: <b>Christine Yu, R.Ph.</b> <b>Regulatory Project Manager, HFD-570</b>		
DATE <b>20 July 2004</b>	IND NO.	NDA NO. <b>21-746</b>	TYPE OF DOCUMENT <b>Original NDA</b>	DATE OF DOCUMENT <b>13 April 2004</b>
NAME OF DRUG <b>Surfaxin (lucinaftant) Intratracheal Suspension</b>		PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>1</b>	DESIRED COMPLETION DATE <b>20 October 2004</b>
NAME OF FIRM: <b>Discovery Laboratories, Inc.</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <input type="checkbox"/> NEW PROTOCOL  <input type="checkbox"/> PROGRESS REPORT  <input type="checkbox"/> NEW CORRESPONDENCE  <input type="checkbox"/> DRUG ADVERTISING  <input type="checkbox"/> ADVERSE REACTION REPORT  <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION  <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 30%;"> <input type="checkbox"/> PRE--NDA MEETING  <input type="checkbox"/> END OF PHASE II MEETING  <input type="checkbox"/> RESUBMISSION  <input type="checkbox"/> SAFETY/EFFICACY  <input type="checkbox"/> PAPER NDA  <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 30%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER  <input type="checkbox"/> FINAL PRINTED LABELING  <input type="checkbox"/> LABELING REVISION  <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE  <input type="checkbox"/> FORMULATIVE REVIEW  <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: <b>Please perform DDMAC review of this NDA. This product is categorized as a NME. Volume 1.1 of the NDA is provided in paper copy with the consult. Please contact me if you have any questions at 827-1051.</b>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <div style="display: flex; justify-content: space-around;"> <input type="checkbox"/> MAIL         <input checked="" type="checkbox"/> HAND       </div>		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

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Christine Yu

7/21/04 05:11:08 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34</b>			FROM: Christine Yu, R.Ph. Regulatory Project Manager, HFD-570	
DATE 16 July 2004	IND NO.	NDA NO. 21-746	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 13 April 2004
NAME OF DRUG Surfaxin (lucinaftant) Intratracheal Suspension		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE 16 October 2004
NAME OF FIRM: Discovery Laboratories, Inc.				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): <b>Trade name review</b>				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Please perform labeling and trade name review for the drug product. This is a NME with orphan drug indication for neonatal respiratory distress syndrome. Volume 1.1 is provided with the paper copy of the consult and includes all labeling. Please contact me if more information is necessary at 301-827-1051. Division goal date is 14 Jan 2005.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND	
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/s/

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Christine Yu

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="text-align: center;">REQUEST FOR CONSULTATION</h2>		
TO (Division/Office): <b>Peter Cooney, Ph. D.</b> <b>Microbiology, HFD-805</b>		FROM: <b>Christine Yu, R.Ph.</b> <b>Regulatory Project Manager, HFD-570</b>		
DATE <b>16 July 2004</b>	IND NO.	NDA NO. <b>21-746</b>	TYPE OF DOCUMENT <b>Original NDA</b>	DATE OF DOCUMENT <b>13 April 2004</b>
NAME OF DRUG <b>Surfaxin (lucinactant)</b> <b>Intratracheal Suspension</b>		PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>1</b>	DESIRED COMPLETION DATE <b>16 October 2004</b>
NAME OF FIRM: <b>Discovery Laboratories, Inc.</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <input type="checkbox"/> NEW PROTOCOL  <input type="checkbox"/> PROGRESS REPORT  <input type="checkbox"/> NEW CORRESPONDENCE  <input type="checkbox"/> DRUG ADVERTISING  <input type="checkbox"/> ADVERSE REACTION REPORT  <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION  <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 30%;"> <input type="checkbox"/> PRE--NDA MEETING  <input type="checkbox"/> END OF PHASE II MEETING  <input type="checkbox"/> RESUBMISSION  <input type="checkbox"/> SAFETY/EFFICACY  <input type="checkbox"/> PAPER NDA  <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 30%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER  <input type="checkbox"/> FINAL PRINTED LABELING  <input type="checkbox"/> LABELING REVISION  <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE  <input type="checkbox"/> FORMULATIVE REVIEW  <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>				
<b>II. BIOMETRICS</b>				
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<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Please perform microbiology review of this new NDA. More specifically, evaluate (b) (4) drug product manufacturing and adequacy of the proposed micro specifications. This is the first pulmonary surfactant for premature infants that does not have a (b) (4). Volumes 1.1 and 2 of 5a-b (section 3.2.P.3) is being provided with the paper copy of this consult. Please contact me for additional information or questions at 301-827-1051.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <div style="display: flex; justify-content: space-around;"> <input type="checkbox"/> MAIL         <input checked="" type="checkbox"/> HAND       </div>		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

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Christine Yu

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 15, 2004

<b>To:</b> Katherine Tsokas Director, Regulatory Affairs	<b>From:</b> Christine Yu, R.Ph. Regulatory Project Manager
<b>Company:</b> Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
<b>Fax number:</b> 215-340-3940	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-340-4699 x-229	<b>Phone number:</b> 301-827-1051
<b>Subject:</b> NDA 21-746 Surfaxin Clinical Information Request	
<b>Total no. of pages including cover:</b> 2	

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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We refer to your NDA 21-746 for Surfaxin (lucinactant) Intratracheal Suspension and have the following request.

For patients who received Surfaxin in study KL4-IRDS-06, provide results, by batch of drug product administered, for the following endpoints:

- Incidence of RDS at 24 hours
- Incidence of RDS-related mortality through 14 days
- Incidence of all-cause mortality through 14 days
- Incidence of air-leak through 7 days
- Number of Surfaxin doses (provide the proportion of patients at each number of doses, not mean or median values)
- Incidences of pulmonary hemorrhage and acquired sepsis through 36 weeks post-conceptual age

It is not necessary to include Exosurf- or Survanta-treated patients, however, doing so would facilitate review of the data.

For the patients who received Surfaxin from more than one drug product batch, count the patient in the results for both the batches he/she received (i.e., count the patient more than once).

Present the data in tabular form. For example:

Endpoint	Batch ABC	Batch CDE	Batch XYZ	Exosurf (optional)	Survanta (optional)
Incidence of RDS					
Incidence of RDS-deaths					
Incidence of all cause deaths					
Incidence of air leak					
No of Surfaxin Doses					
% who received 1 dose					
% who received 2 doses					
Etc.					
Pulmonary hemorrhage					
Acquired sepsis					

It is not necessary to perform statistical comparisons of the results between batch groups at this time.

If you have any questions regarding this facsimile correspondence, please contact Christine Yu, R.Ph., Regulatory Project Manager @ 301-827-1051.

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/s/

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Christine Yu  
7/15/04 03:05:27 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-746

Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

Attention: Christopher J. Schaber, Ph.D.  
Executive VP, Drug Development & Regulatory Compliance  
Chief Operating Officer

Dear Dr. Schaber:

Please refer to your April 13, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant) Intratracheal Suspension.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 12, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Submit 6-month follow-up safety data, as requested by the Agency during the pre-NDA meeting on June 13, 2003.
2. We note a potentially serious compliance problem with the manufacturing site for the drug product. 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 of batches used in clinical trials, stability studies, and to-be-marketed drug product. Include certificates of analysis for the drug product batches supporting this NDA.
3. Stability data for the drug product submitted with the NDA are inconsistent with our previous advice provided during the pre-NDA meeting on June 13, 2003. Provide the following.
  - a. Submit updated stability results to include 6 month, 9 month and other available data points as soon as possible.
  - b. Provide statistical evaluation of changes-with-time for all parameters with emphasis on the activity-related parameters and impurity profile.
  - c. Submit tightened proposed acceptance criteria reflective of the data.



4. 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 using "conform" and "does not conform" format.
5. 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. Submit revised specifications, accordingly.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the requested information and note the following:

6. Provide a list of countries, if any, in which application for marketing is pending or has been approved.
7. You did not apply uniform pagination throughout the application and did not provide a Table of Contents with page references. This requires additional time to locate and review the pertinent information which impedes timely review. Include consecutive page numbers and provide the customary Table of Contents with references to volumes and pages in your future submissions.

Please respond to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Badrul Chowdhury  
6/25/04 04:05:43 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-746

Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

Attention: Christopher J. Schaber, Ph.D.  
Executive VP Drug Development & Regulatory Compliance

Dear Dr. Schaber:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Surfaxin (lucinactant) Intratracheal Suspension 30 mg/mL
Review Priority Classification:	Standard (S)
Date of Application:	April 13, 2004
Date of Receipt:	April 13, 2004
Our Reference Number:	NDA 21-746

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 12, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 13, 2005.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for studies in children outside of the neonatal population for this application.

In the cover letter of your NDA submission, you requested priority review status. However, you did not submit convincing evidence that Surfaxin is a significant improvement compared to

currently marketed products in the treatment, diagnosis, or prevention of a disease. Additionally, you did not submit sufficient data as requested by the Agency during the pre-NDA meeting on June 13, 2003. Therefore, we have concluded that this application should receive a standard review.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary & Allergy Drug Products, HFD-570  
Attention: Document Room 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call Ms. Christine Yu, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Badrul Chowdhury  
5/17/04 04:24:02 PM

## MEMORANDUM OF TELECONFERENCE

DATE: October 27, 2004  
APPLICATIONS: NDA 21-704, IND 40,287  
DRUG NAME: Surfaxin (lucinactant) Intratracheal Suspension  
SPONSOR: Discovery Laboratories, Inc.

Participants: Katherine Tsokas, Director, Regulatory Affairs  
Chris Schaber, Ph.D., Exec VP, Drug Development & Regulatory Compliance  
Robert Segal, M.D., VP, Clinical Research & New Drug Evaluation  
Tony Killian, M.D., VP, Medical Monitor

Phone: 215-340-4699

FDA: Division of Pulmonary & Allergy Drug Products, HFD-570  
Harry Gunkel, M.D., Medical Reviewer  
Peter Starke, M.D., Medical Team Leader  
Sue-Jane Wang, Ph.D., Biostatistics Team Leader (Actg)  
Badrul Chowdhury, M.D., Ph.D., Director  
Christine Yu, R.Ph., Regulatory Project Manager

The Division stated that they initiated this teleconference to resolve issues arising from two submissions under IND 40,287 and NDA 21-746, both applications for Surfaxin, as well as a question from Discovery relayed by phone.

1. August 26, 2004, submission 218 to IND 40,287, a proposed Phase 3b study

In response to the Division's request for clarification, Discovery stated that it had been their original intention to submit results of the proposed 3b study during the review of NDA 21-746. The Division noted that the study could not realistically be conducted and results submitted during the review time remaining. In the unlikely event that the final study report would be submitted, it would extend the review clock. The Division asked if the protocol had been finalized. Discovery responded that the final protocol has not yet been completed; accordingly, the study has not been started. The Division stated that under those circumstances, it would be premature to discuss a study to possibly add new information to the package insert before there is a package insert. Although it is Discovery's decision, the Division recommended that the company conduct the phase 3b after the Agency has taken an action on NDA 21-746.

Discovery stated that they will wait until the Agency takes an action on the NDA before conducting the study.

2. Submission dated October 8, 2004, to NDA 21-746, Response to Request for Information.

On September 24, 2004, the Division had requested that Discovery "Submit the interim statistical analysis reports for the primary co-endpoints originally defined and at the time of changing the primary efficacy co-endpoints." In a submission dated October 8, 2004, Discovery responded that, "There were not any formal interim analyses conducted by the DSMB (Data Safety Monitoring Board)...As such, no reports of such analyses exist." However, in NDA 21-746, the study report of KL4-IRDS-06 (Module 5, volume 1.1, paragraph 11.4.2.3, page 63) contains the statement, "There were two formal interim efficacy analyses performed on the primary endpoints by the DSMB." Also, during the pre-NDA meeting for IND 40,287 on June 13, 2003, the statistical consultant for Discovery had indicated that an interim analysis had been performed. The Division requested additional clarification of these discrepancies and again requested the reports.

Discovery responded that the study had not planned for an interim analysis and that they (Discovery) did not perform one. Discovery stated, however, that the DSMB performed interim analyses as needed for their safety monitoring role, but did not unblind the data. The Division again pointed to the information in the NDA about results of interim analyses and asked Discovery to clarify this discrepancy. Discovery stated that they would look into it and follow up.

The Division further specified that they were looking for information about when the interim analyses were performed in relation to the time when the primary endpoint was changed. The Division requested minutes from all DSMB meetings. Discovery agreed to submit the minutes from the DSMB meetings.

Post-teleconference note: Discovery submitted the requested DSMB information to the NDA on November 1, 2004.

- 3.



clarification, the Division stated that the new study can be submitted to the existing IND 40,287.

The teleconference concluded at this time.



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 14, 2003

**To:** Christopher Schaber  
Exec VP, Drug Dvm &  
Regulatory Compliance

**From:** Christine Yu, R.Ph.   
Sr. Regulatory Project Manager

**Company:** Discovery Laboratories, Inc.

Division of Pulmonary & Allergy Drug  
Products

**Fax number:** 215-340-3940

**Fax number:** 301-827-1271

**Phone number:** 215-340-4699 x130

**Phone number:** 301-827-1051

**Subject:** IND 40,287 Surfaxin KL4-IRDS-06  
Response to submissions dated August 19 and October 31, 2003

**Total no. of pages including cover:** 2

**Comments:**

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**Document to be mailed:**

☐ YES

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We reference your protocol KL4-IRDS-06 entitled, "A multi-national, multi-center, randomized, controlled prophylaxis superiority trial of the safety and effectiveness of Surfaxin compared to Exosurf in the prevention of RDS in premature neonates." In response to your submissions 178 and 190 dated August 19 and October 31, 2003, we have the following comments regarding the four options you have proposed for performing the primary statistical analysis.

It was our intent that the following co-primary endpoints would be used for the statistical analysis of KL4-IRDS-06:

- Incidence of RDS at 24 hours, *and*
- RDS-related mortality through 14 days and/or air leak through 7 days of age.

Both the "incidence of RDS at 24 hours" and the "composite of RDS-related mortality through 14 days and/or air leak through 7 days" would need to be statistically significant at a 2-sided 5% alpha level. The second co-primary endpoint "RDS-related mortality through 14 days and/or air leak through 7 days of age" was intended to be a true composite endpoint. We requested secondary analyses of the individual components of the composite endpoint in order to facilitate the clinical interpretation of the data. You had agreed to this approach, and we believe that the second co-primary endpoint described above remains appropriate for the statistical analysis of KL4-IRDS-06.

However, after extensive discussion, we have determined that two of the alternatives for analysis included in your October 31, 2003, proposal would also be acceptable. These are:

1. Move "air leak through 7 days" from being a part of the co-primary composite endpoint to being a secondary endpoint. Under this scenario, the co-primary endpoints for the statistical analysis of KL4-IRDS-06 will be:
  - a. Incidence of RDS at 24 hours ( $p \leq 0.05$ ), *and*
  - b. RDS-related mortality through day 14 ( $p \leq 0.05$ ).
2. Change the co-primary composite endpoint "air leak through day 7 and/or RDS death through day 14" to two separate co-primary endpoints, either of which could "win" without analyzing their occurrence as a composite. This would require, as you have proposed, adopting means to deal with multiplicity issues. Under this scenario, the co-primary endpoints for the statistical analysis of KL4-IRDS-06 will be:
  - a. Incidence of RDS at 24 hours ( $p \leq 0.05$ ), *and*
  - b. RDS-related mortality through day 14 ( $p \leq 0.045$ ) *or* air leak through day 7 ( $p \leq 0.005$ ).

We believe that either the original endpoints (including air-leaks and death due to RDS as a true composite) or the two options above are acceptable. We also believe that it may be more difficult for you to show efficacy using the two alternative options you have proposed. We trust that this response to your October 31, 2003, proposals will allow you to finalize the statistical analysis plan for KL4-IRDS-06 before the data are unblinded.

If you have any questions regarding this facsimile correspondence, please contact Ms. Christine Yu @ 301-827-1051.

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/s/

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Christine Yu  
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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 7, 2003

**To:** Christopher Schaber  
Exec VP, Drug Dvm &  
Regulatory Compliance

**From:** Christine Yu, R.Ph.   
Sr. Regulatory Management Officer

**Company:** Discovery Laboratories, Inc.

Division of Pulmonary & Allergy Drug  
Products

**Fax number:** 215-340-3940

**Fax number:** 301-827-1271

**Phone number:** 215-340-4699 x130

**Phone number:** 301-827-1051

**Subject:** IND 40,287 Surfaxin  
Response to submission 185 entitled "Proposal for the provision of drug product  
stability for the NDA filing for Surfaxin in RDS."

**Total no. of pages including cover:** 2

**Comments:**

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other action based on the content of this communication is not authorized. If you have  
received this document in error, please notify us immediately by telephone at 301-827-1050.  
Thank you.**

In response to submission dated October 3, 2003, serial number 185, we have the following comments.

1. The stability data from (b) (4) you have proposed to submit are acceptable.
2. Regarding stability data from (b) (4)
  - a. As we have indicated during the pre-NDA meeting on June 13, 2003, *6 months of stability data for at least 3 batches of the drug product manufactured at the new facility are needed at the time of NDA submission.* However, since you will have supportive stability data from (b) (4) (proposal #1), 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. Provide at least three (3) additional months (nine months total) of long-term primary stability data for two batches of 30 mg/mL and two batches of 10 mg/mL manufactured at (b) (4) during the NDA review period.

If you have any questions regarding this facsimile correspondence, please contact Ms. Christine Yu @ 301-827-1051.

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Office of Drug Evaluation ODE II

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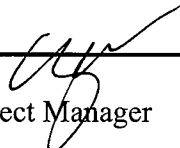
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**DATE:** October 14, 2003

**To:** Christopher Schaber  
Exec VP, Drug Dvm &  
Regulatory Compliance

**From:** Christine Yu, R.Ph.   
Sr. Regulatory Project Manager

**Company:** Discovery Laboratories, Inc.

Division of Pulmonary & Allergy Drug  
Products

**Fax number:** 215-340-3940

**Fax number:** 301-827-1271

**Phone number:** 215-340-4699 x130

**Phone number:** 301-827-1051

**Subject:** IND 40,287 Surfaxin  
Response to submissions 174, 175, and 184

**Total no. of pages including cover:** 2

**Comments:**

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We have completed review of your submissions 174, 175, and 184 and have the following comments.

Submission 174 dated July 31, 2003

"Proposal to Submit the Surfaxin New Drug Application (NDA) Before Completion of the 6-Month Follow-up Data Collection."

We reiterate our position that complete 6-month data will be necessary in order for the Division to make a determination of safety and efficacy. Therefore, we recommend that you not submit the application until the 6-month data have been analyzed. Although the Agency may file the application with less than complete 6-month data, it is most likely that the incomplete database would not be sufficient to allow a confident determination of safety and efficacy.

← relayed by  
phone 150  
to C. Schell  
9/25/03

Submission 175 dated August 12, 2003

"Proposal to use a 3- to 4-week old kitten model for the 14-day animal toxicology study of Surfaxin."

Three to four week old kittens are not considered newborn because they are of weaning age. Conduct this study using younger kittens or other species with the appropriate age.

Submission 184 dated September 25, 2003

"Proposal to use a 14- to 28-day old kitten model for the 14-day animal toxicology study of Surfaxin."

Your proposal to use 14-day old kittens in the 14-day toxicology study is acceptable.

If you have any questions regarding this facsimile correspondence, please contact Ms. Christine Yu, R.Ph., Sr. Regulatory Management Officer @ 301-827-1051.

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/s/

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Christine Yu  
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CSO



## MEETING MINUTES

DATE: June 13, 2003  
TIME: 3:30 - 5:00 PM  
TYPE: Pre-NDA  
LOCATION: Parklawn Conference C  
APPLICATION: IND 40,287  
DRUG NAME: Surfaxin (lucinactant) Intratracheal Suspension  
INDICATION: Prophylaxis of neonatal Respiratory Distress Syndrome (RDS)  
IMTS#: 10499

SPONSOR: Discovery Laboratories, Inc.

Represented by: Vincent Benn, Ph.D., VP, Clinical Operations  
R. Christopher Cavalli, Ph.D., Sr. Dir., Analytical & Technical Services

(b) (4)

Janusz Gadzinowski, M.D., Lead Investigator- Central Europe

(b) (4)

(b) (4)

(b) (4)

Adam Rumage, Manager, Regulatory Affairs  
Christopher Schaber, Exec. VP, Drug Dvm & Regulatory Compliance  
Robert Segal, M.D., Sr. VP, Clinical Research & New Drug Evaluation  
Huei Tsai, Ph.D., Sr. VP, Biometrics

FDA attendees: Division of Pulmonary & Allergy Drug Products, HFD-570

Chong Ho Kim, Ph.D., CMC Reviewer  
Eugenia Nashed, Ph.D., CMC Reviewer  
Guirag Poochikian, Ph.D., CMC Team Leader  
Huiqing Hao, Ph.D., Pharmacologist  
Joseph Sun, Ph.D., Supervisory Pharmacologist  
Emmanuel Fadiran, Ph.D., Clinical Pharmacology & Biopharmaceutics TL  
Sue-Jane Wang, Ph.D., Mathematical Statistician  
Thomas Storch, M.D., Medical Reviewer  
Eugene Sullivan, M.D., Medical Team Leader (Acting)  
Marianne Mann, M.D., Deputy Director  
Badrul Chowdhury, M.D., Ph.D., Director  
Donald Collier, Regulatory Information Specialist  
Christine Yu, R.Ph., Regulatory Management Officer

Edward Nevius, Ph.D., Director, Division of Biometrics II, HFD-715  
Eric Duffy, Ph.D., Director, Division of New Drug Chemistry II, HFD-820  
Robert Meyer, M.D., Director, Office of Drug Evaluation II, HFD-102

Discovery submitted a request for a pre-NDA meeting on April 17, 2003. The briefing packages were received May 16, 2003, and contained 20 questions for discussion.

Agenda (based on order of "Summary of Issues and Questions" included in the briefing package)

General (Regulatory)

Chemistry, Manufacturing, and Controls (CMC)

Preclinical

Clinical & Statistical

Guidances for Industry referenced during the meeting

Guidances represents the Food and Drug Administration's (FDA's) current thinking on a topic.

It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

Minutes

The Division's slides include Discovery's questions (in normal font), followed by the Division's responses noted in Italics.

**General section**

**Question 1**

Discovery intends to submit the NDA in the CTD format as established by ICH guidelines (sic)...

- *This is acceptable as long as the FDA Guidance, "M4: Common Technical Document for the Registration of Pharmaceuticals for Human Use" and its sub-parts are adhered to.*
- *Particular attention should be paid to the indexing levels and labeling of sections.*
- *The sample CTD TOC looks quite adequate, with the assumption that this is a top-level listing and does not represent the full depth of the final product.*

## General section

### Question 2

Discovery would like to confirm that the NDA would be subject to a priority review as Surfaxin is intended to treat a severe, life-threatening, orphan indication.

*The review classification of an NDA, i.e., either standard or priority, is assigned by the Division after submission of the NDA. An NDA may be designated for priority review when the drug product, if approved, would be a significant improvement compared to marketed products [Guidance for Industry: Fast Track Drug Development - Designation, Development, and Application Review, September 1998].*

## General section

### Question 3

Discovery plans to pursue (b) (4) indications and request comments on this pursuit.

*The primary objectives of your pivotal RDS trial, multinational, multicenter, randomized, masked, controlled prophylaxis superiority trial of the safety and effectiveness of Surfaxin® (lucinactant) compared to Exosurf® (colfosceril palmitate) in the prevention of Respiratory Distress Syndrome (RDS) in premature neonates (KL4-IRDS-06) are:*

- 1) to determine the difference in efficacy between Surfaxin and Exosurf in the prevention of RDS in premature neonates; and*
  - 2) to assess the relative safety of Surfaxin vs Exosurf.* (b) (4)
- (b) (4)

**General section**

**Question 3- Additional Comments**

- *KL4-IRDS-06 cannot serve as a pivotal trial to establish (b) (4) for RDS. The Division notes that Discovery has agreed that KL4-IRDS-06 has been designed to be a prophylactic study and to remove (b) (4) from the Investigators Brochure and the Informed Consent (Teleconference March 4, 2002).*
- *At your request, the Division can provide comments on the design of additional proposed trials if you plan to pursue (b) (4) for RDS.*

**General section**

**Question 4**

Discovery would like to confirm that there are no issues regarding the current Surfaxin trademark.

*"Surfaxin" will be evaluated by the Office of Drug Safety, including a trade name review, when the NDA has been submitted. All proposed labels and labeling should be submitted with the NDA.*

**General section**

**Comments from Office of Drug Safety**

- a) *We encourage you to evaluate risks that may be associated with the use of Surfaxin and propose ways to manage or reduce these risks. Plans for risk management should be included in Module I of the Common Technical Document for the NDA application.*
- b) *If there are plans for risk management activities that include risk communication involving patient education and information (such as a PPI, Medication Guide or other informational/educational products), these materials should be clearly noted as such and included in the risk management plan section.*

**General section**

**Comments from Office of Drug Safety**

- c) *If there is any information on product medication errors from clinical studies under the IND, ODS requests that this information be submitted in the NDA.*

**CMC section**  
**Question 5**

Discovery plans to submit the CMC portion of the new drug application 90 – 120 days prior to the submission of the remainder of the NDA.

*A complete CMC portion of the NDA can be submitted 90-120 days prior to the whole package of the NDA. However, the submission must be complete and should address the following issues.*

**CMC section**  
**Question 5- Comments**

*According to your fax dated June 4, 2003, your contract manufacturer, (b) (4), has had a long history of cGMP violations, and you have indicated your plans to move the Surfaxin drug product manufacturing to another facility. CMC issues related to a manufacturing site change, i.e., manufacturing, packaging, labeling and testing (release and stability) of the drug product must be fully addressed.*

**CMC section**  
**Question 5- Comments**

*Provide comparative data on manufacturing, physico-chemical and biological properties of the drug product, and release and stability data for drug products manufactured at the "old" and "new" facilities.*

The Division stated that it would be important for interpreting the clinical studies to show that the same drug will be manufactured at the new facility.

**CMC section**  
**Question 6**

Discovery requests an allowance to submit the NDA with two stability batches containing 18 and 12 month data only and would like to confirm this is acceptable.

*Since the above stability batches were manufactured at the old site, it is considered a supportive stability data. Three batches of 6 month long term and accelerated stability data for drug product manufactured at the new site should be submitted. The long term data have to be updated during the review process.*

Discovery stated that if they choose to remain with (b) (4), they would have two stability batches with 24 and 18 months of data.

The Division stated that although it is ultimately the company's decision which facility would be used, if Discovery chooses another manufacturer, the two batches from (b) (4) would be supportive data only. A minimum 6-months stability data from 2 batches manufactured at the new facility would be needed at the time of the NDA submission. The two stability batches from (b) (4) can be considered acceptable as a third batch.



**CMC section**  
**Question 7**

Pursuant to 21 CFR 314.50(d)(1)(ii)(a), Discovery proposes to submit a detailed narrative of the manufacturing process and one executed batch record in lieu of a master batch record.

*The proposed one executed batch record should be from the new manufacturing facility. The manufacturing parameters, components of the drug product, and the manufacturing equipment should be identical or comparable to the old manufacturing process.*

**CMC section**  
**Question 8**

Discovery wishes to confirm that the CMC program appears adequate for approval assuming the below FDA requests are addressed in an acceptable manner.

*Without adequate data and information, it is premature to discuss approvability of the CMC section at this time. Address the following issues:*

- *We have provided you previously with numerous comments (see letters dated February 9, 1995, March 10, 1997 and facsimile transmissions dated November 3, 1999 and January 24, 2000). Address all the remaining issues adequately.*



Because response to previous CMC comments provided were noted that they "will be done," the Division stated that they were not able to provide more definitive recommendations. Further CMC discussions may be possible when Discovery can provide the data.

## **CMC section**

### **Question 8- Comments continued**

- *The proposed specifications (for DS and DP) are not adequate.*
- *Include a biological activity test and acceptance criterion in the release and stability specifications.*

Discovery stated that they believed that the surfactometer is a better indicator of biological activity and asked about substituting the surface tension test for the biological activity test (BAT).

The Division responded that the BAT is currently the most appropriate for assuring that the peptide is active. Surface tension testing measures a physicochemical property of the drug product mixture and does not measure the biological activity. The most reliable BAT's that are used for other pulmonary surfactants is the test on premature rabbits and the rat lung tests. In the later phases of drug product development, the company could develop physical characteristic test(s) and link relationship to biological activity, but at the earlier stages of development, the Agency recommended that the BAT be established as a standard which can be referenced later.

The Division continued by stating that comparability of drug product batches used for preclinical and clinical studies and to-be-manufactured batches have to be demonstrated using complete set of attributes, including the BAT. Biological activity is a critical criterion and should be monitored during stability. The BAT would be performed in addition to the proposed in-vitro surfactometer test. All methods should be adequately validated.

**CMC section**  
**Additional Comments**

- a) *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.*
- b) *The comparability data have to be thorough and present actual data for all parameters, including the surface tension, detailed physicochemical characterization and biological activity. Additional meeting or teleconference may be requested, as needed.*

**CMC section**  
**Additional Comments**

- c) *Provide assurance that the same drug substance and other drug product ingredients will be used in the new facility.*
- d) *For synthetic peptide substances, refer to the "Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances, November 1994".*

## **Preclinical section**

### **Question 9**

Discovery would like to confirm that, once the two FDA requested toxicity studies in young, nonrodent species are complete, the preclinical program is sufficient to support a NDA for of RDS.

*We concur. The two new born studies (3-4 week old) with 14 day dosing in 2 different species can be used to support the NDA.*

Discovery asked if 14-day toxicity study using 5 weeks old rabbits would be acceptable as one of two 14-day studies in newborn animals.

The Division replied that the acceptability 5-week old rabbits would be determined by how "newborn" is defined in rabbits. As a follow-up, the Division now provides the following clarification.

(b) (4) rabbit weaning age was reported as day 35.

Therefore, 5 weeks old rabbits are not considered newborn. The Division's previous agreement on the newborn age of 3-4 weeks referred to larger species such as dogs, but not rabbits. The Division recommends that Discovery repeat the rabbit 14-day study with rabbits of appropriate age or using other age-appropriate animal species.

## **Preclinical section**

### **Question 10**

Discovery requests the possibility of submitting the preclinical portion of the NDA 90-120 days prior to the submission of the remainder of the NDA.

*FDA regulations do not provide for presubmission of preclinical portions of the NDA. Final reports of preclinical studies may be submit to the IND.*

## Clinical section

### Question 11

Discovery intends to provide information from its neonatal programs (data from completed studies, not including ongoing studies) as part of this application, and is not planning to include data from other studies (i.e., the ARDS trials). We wish to confirm that this is acceptable.

- *Excluding Surfaxin data from ongoing neonatal studies and from the ARDS trials is not acceptable.*
- *21 CFR 314.50 describes the required content of an NDA:  
The application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source.*

## Clinical section

### Question 11- Additional Comments

21 CFR 314.50(d)(5) states:

- (ii) Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol, and a brief description of the results and status of the study.
- (iv) A description and analysis of any other data or information relevant to an analysis of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

## **Clinical section**

### **Question 11- Additional Comments**

- *The Division requires data from the ongoing newborn and adult studies to conduct our review of Surfaxin safety. The Division cannot ignore the possibility that these studies, when analyzed individually and in conjunction with the preterm newborn studies, could yield important safety information.*
- *The Division's review of efficacy for your proposed NDA submission will focus on the preterm newborn.*

## **Clinical section**

### **Question 12**

Discovery intends to submit the NDA prior to the completion of the one-year follow-up data and provide periodic amendments containing this information during the review cycle.

*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (Guidance for Industry, May 1998) states: "When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all available data be examined for their potential to either support or undercut reliance on a single multicenter trial."*

**Clinical section**

**Question 12- Additional Comments**

- *Your submission of October 29, 2001 (serial 97) described your intention to lock the KL4-IRDS-06 database in two stages. The Division is not aware that this submission contained a statement of your intention to submit the NDA prior to the completion of the one-year follow-up data.*
- *Your NDA submission must contain complete data for the 36 week PCA and the 6 month corrected age time points. If your NDA contains complete data for these two time points, submission of one year follow-up data as periodic amendments is acceptable to the Division.*

**Clinical section**

**Question 13**

Discovery plans to supply the required case report forms in paper format and seek to confirm that this is acceptable.

*The paper format is acceptable.*

## Clinical section

### Question 14

Discovery would like to confirm that the Independent DSMB SOP provided to IND 40,287 on March 5, 2002 (serial no. 114) in conjunction with Discovery's response to Agency comments on the procedure provided to IND 40,287 on April 30, 2003 (serial 161) is acceptable.

- *You have accepted the Division's comments regarding The Data Safety Monitoring Board standard operating procedure for unblinding of individual patient data due to serious adverse events.*
- *However, as of this date, the Division has not received the response of (b) (4) DSMB Chairperson, to the Division's comment regarding the final stopping rule.*

In response to the second bullet above, Discovery stated that they will submit (b) (4)' response.

## Clinical section

### Question 15

Discovery would like to confirm that the Adjudication Committee SOP provided to IND 40,287 on April 29, 2002 (serial no. 119) in conjunction with Discovery's response to Agency comments on the procedure provided to IND 40,287 on April 30, 2003 (serial 161) is acceptable.

- *From Division fax dated February 24, 2003. to Discovery:*  
*"How an infant who has a diagnosis of RDS and dies as a result of pulmonary hemorrhage or severe intracranial hemorrhage will be classified."*
- *Per the Adjudication Committee SOP definition in submission 119 dated April 29, 2002, & submission 161 dated April 30, 2003:*  
*An infant who dies as a result of pulmonary hemorrhage will be classified as a RDS-related death if such an infant has RDS that has not resolved prior to the pulmonary hemorrhage.*

## Clinical section

### Question 15- Additional Comments

- From Discovery submission 161 dated April 30, 2003:  
*In the case of severe intracranial hemorrhage, death will be classified as being RDS-related if the RDS is clinically significant enough that it is likely to contribute to this complication. In the less frequent situation where an infant had evidence of RDS that subsequently resolved or significantly improved, then had an intracranial hemorrhage (i.e., the hemorrhage is not proximately associated with the RDS), that infant will be classified as Non-RDS-related death. [Please note that the diagnosis of RDS can occur at any time prior to the death of the infant (the infant does not have to meet the 24 +/- 4-hour RDS definition)].*

## Clinical section

### Question 15- Additional Comments

#### The Division's comments:

- *Discovery should classify a patient who dies with any evidence of RDS in the first 14 days of life as RDS-related mortality as agreed in discussions with the Division (Teleconference of March 4, 2002).*
- *The membership of the Death Adjudication Committee (Discovery Serial 161 April 30, 2003), including medical specialty and geographic location, is acceptable to the Division.*

Discovery, in response to the first bullet above, stated that it is difficult to differentiate death from RDS versus death from other complications of prematurity. Classifications are based on the current practices of neonatologists.



## **Clinical section**

### **Question 16**

Discovery would like to confirm that the KL4-IRDS-06 SAP, including the format of the data tables and listings, provided to IND 40,287 on April 29, 2002 (serial no. 119) in conjunction with Discovery's response to Agency comments on the SAP provided to IND 40,287 on April 30, 2003 (serial no. 161) is acceptable.

*In the Division's fax dated March 06, 2002, we acknowledged that "the final statistical model will include birth-weight, gender, and region in order to identify the independent effect of surfactant treatment." Discovery was asked to clearly define the region a priori in the protocol. We also noted that the analyses including "terms for the interaction of surfactant treatment with birth-weight and center, as well as terms for other important baseline variables that might be found to be significantly different between the two treatment groups" will be considered exploratory analyses only. "The final statistical model will be the basis for the definitive primary efficacy evaluation."*

Discovery indicated agreement with the statement in the slide above.

## **Clinical section**

### **Question 16- Additional Comments**

- *Accordingly, Tables 6.x and 7.x need to be changed to reflect the above point. The overall treatment effect after adjusting for the pre-specified factors for the primary efficacy evaluation needs to be tabulated with its corresponding p-value and nominal 95% CI.*
- *For future NDA review purposes, we request that you submit an amendment that contains all the agreed-upon changes to the protocols as the final statistical analysis plan.*

The Division stated that the final statistical analysis plan (SAP) should also contain, for example, the DSMB stopping rules, methodology for multiplicity adjustment (not in SAP to date). More

specifically, each co-primary endpoint is to be analyzed at a 2-sided 5% level. In addition, the standard subgroup reporting by gender and by race should be included in the final NDA reports.

**Clinical section**

**Question 17**

Discovery would like to confirm that the KL4-IRDS-02 statistical analysis plan (SAP), including the format of the data tables and listings, provided to IND 40,287 on April 24, 2003 (serial no. 160) is acceptable.

*The KL4-IRDS-02 trial will mainly be a supportive study providing safety information.*

**Clinical section**

**Question 18**

Discovery expects to supply all clinical data generated for the studies in the form of SAS datasets, along with the applicable SAS programs for data listings and data tables, and request confirmation that this is acceptable.

*The proposed clinical data format is acceptable. The applicable SAS program should include those for the primary efficacy analysis and the secondary efficacy analysis.*

The Division reminded Discovery that all data must be submitted in Version 5 SAS Transport Format, as per Guidance for Industry, "Providing Regulatory Submissions in Electronic Format- General Considerations."

## **Clinical section**

### **Question 19**

Discovery plans to submit the ISS (Attachment 8) and the ISE (Attachment 9) in the format provided in this submission and requests confirmation that this is acceptable.

*The proposed formats are acceptable.*

*We have the following general comments regarding the content of these documents.*

## **Clinical section**

### **Question 19- ISS Comments**

- *You must include safety data from the ARDS trials*
- *You should present the data for preterm newborns with RDS, newborns with MAS, and adults separately.*
- *You should construct shift tables with clinically appropriate upper and lower limits for clinical observations and laboratory studies. The limits for mean change from baseline and for outliers should be pre-specified before the data is analyzed.*
- *You should categorize race / ethnicity as Native American, Asian, Black, Caucasian, Hispanic/Latino, and other or unknown.*
- *You should add cyanosis, bradycardia, and tachycardia to the adverse reactions associated with dose administration.*

## **Clinical section**

### **Question 19- ISE Comments**

- You must analyze primary and secondary endpoints by study center, birth weight, gender, and race/ethnicity.
- You should separately analyze FiO<sub>2</sub>, MAP and OI for patients with ventilation modes other than conventional mechanical .
- Birth weight categories should be: < 600, 600-700, 701-800, 801-1000, 1001-1250, >1250g.
- Race / ethnicity categories should be: Native American, Asian, Black, Caucasian, Hispanic / Latino, other / unknown.
- You should add to maternal history: ≥ 35 years age, prenatal care, pre-eclampsia and eclampsia, STD and HIV, illicit drugs
- You should add to neonatal demographics: breech presentation, C-section total (emergency and non-emergency), resuscitation with epinephrine and/or chest compressions.
- You should include hearing under secondary parameters.

## **Clinical section**

### **Question 20**

As the pursued indication is acute and in accordance with 21 CFR 314.50(f)(2), Discovery requests a waiver from providing case report forms for patients who have not completed a study because of an adverse event and would like to provide complete case report forms in the NDA only for patients who have died.

*"The application is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drug or placebo. This requirement may be waived by the FDA for specific studies if the case report forms are unnecessary for a proper review of the study." 21 CFR 314.50(f)(2)*

## **Clinical section**

### **Question 20- Additional Comments**

- *Discovery must include case report forms for patients who did not completed the study because of an adverse event as specified in 21 CFR 314.50(f)(2).*
- *Adverse events associated with dropouts are an essential and necessary part of the Division's review of Surfaxin safety.*

The meeting was adjourned at this time.

## MEMORANDUM OF INTERNAL MEETING

**DATE:** April 8, 2003  
**TIME:** 8:30 - 9:30 AM  
**LOCATION:** Parklawn 10B-45 CR  
**APPLICATION:** IND 40,287 (b) (4) Surfaxin (lucinaquant)  
**SPONSOR:** Discovery Laboratories, Inc.  
(b) (4)

**PARTICIPANTS:** Division of Pulmonary & Allergy Drug Products, HFD-570

Chong Ho Kim, CMC Reviewer  
Guirag Poochikian, CMC Team Leader  
Thomas Storch, Medical Officer  
Eugene Sullivan, Medical Team Leader  
Marianne Mann, Deputy Director  
Badrul Chowdhury, Director  
Christine Yu, Regulatory Project Manager

Office of Drug Evaluation II, HFD-102

Robert Meyer, Director  
Leah Ripper, Associate Director for Regulatory Affairs

Office of Pharmaceutical Science, Microbiology Team, HFD-805

Paul Stinavage, Microbiologist  
Peter Cooney, Supervisory Microbiologist

Discovery contacted the (b) (4) District Office (b) (4) on March (b) (4), requesting Surfaxin lots be exempted from (b) (4) voluntary recall procedures. (b) (4), the sole contract manufacturer of Surfaxin, has a history of noncompliance with cGMPs. Discovery stated that the Surfaxin lots in question are the only available drug product source and are being utilized currently in clinical trials. They stated that the lots are not contaminated and requested exemption from the recall, so that the ongoing multi-national Phase III trial would not be irreparably disrupted. The (b) (4) District requested the Division's guidance in considering exemption of the Surfaxin lots from (b) (4) recall.

Information received:

- March (b) (4) e-mail from (b) (4) which included a letter from Discovery requesting exemption.
- March (b) (4) e-mail from (b) (4) giving a brief chronology of (b) (4) recent recall of drug products manufactured in (b) (4).
- April (b) (4) facsimile from (b) (4) of batch records for Surfaxin lots.
- April (b) (4) e-mail from (b) (4) which included the Establishment Inspection Report (EIR) from the (b) (4) site inspection.
- Certificates of Analysis (COAs) before release of Surfaxin batches from Discovery.

The investigational product was filled in (b) (4) facility has had a history of cGMP difficulties, including a series of failed media fill simulations, and now

has chosen to voluntarily recall all products produced at the facility since December 7, 2001. The investigational product is intended for use in premature and full-term infants (IND 40,287) (b) (4)

(b) (4) A major portion of Surfaxin is used in the clinical trial for premature infants.

The Division requested an assessment from Drs. Cooney and Stinavage of the microbiology staff to determine whether the lots in question are contaminated and whether the use of such products in the target population would increase safety risk. After review of the data provided by (b) (4), Discovery, and the (b) (4) district, the microbiologists concluded that the lots in question are very unlikely to be contaminated and the use of the product does not represent undue risk to the target population for the following reasons:

- Surfaxin manufacture dates (spanning (b) (4)) are bracketed by three media fills that did not demonstrate contamination (b) (4) page 14 of EIR.
- Results of USP sterility tests performed on 4 product lots indicate that all passed USP criteria for a sterile product. The USP sterility test is one of the main microbiological criteria that sterile investigational products are required to meet.
- The minimum media fill lot size at (b) (4) (EIR, page 17 of 90). The maximum frequency of contamination in (b) (4) 6 positive vials. Other (b) (4) media fills with positive contamination were as follows: 3 positives, 3 positives, 2 positives, 1 positive, 2 positives, and 1 positive. (The rates would be significantly higher if the media fill process was contaminated.)

### DECISIONS

The Division decided that, based on the data provided and the microbiologists' assessments, there is no significant additional safety risk to the study subjects. It was noted in discussions that for most IND's, there is no inspection to assure compliance with cGMPs in the manufacture of these investigational agents. Further, at least one of the earlier surfactants studied and approved were not manufactured to be sterile during their clinical investigation phase of development. From the Division's perspective, it would be acceptable to exempt the specified Surfaxin lots from (b) (4) recall.

<u>Action Items</u>	<u>Responsible Person</u>	<u>Date</u>
1. Relay the Division's decision to (b) (4)	Christine Yu	Conveyed 4/8/03 by phone to (b) (4)
2. Memorandum of internal discussion copied to (b) (4) office	Christine Yu	Faxed 4/22/03
3. Convey the Agency's concern, that given (b) (4) history of non compliance with cGMPs, Discovery should consider an alternative manufacturing site(s).	Christine Yu	Completed 4/11/03 by phone conversation with Christopher Schaber.

### Post-meeting Notes

During the April 11, 2003, phone conversation, Christopher Schaber (Executive VP, Drug Development & Regulatory Compliance, Discovery) informed me that (b) (4),

Internal meeting April 8, 2003

Page 3

(b) (4) notified Discovery on April 9, 2003, that the specified Surfaxin lots have been exempted from (b) (4) recall.



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/s/

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Christine Yu  
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Office of Drug Evaluation ODE II

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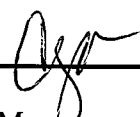
**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** February 24, 2003

**To:** Christopher Schaber  
Executive Vice President  
Drug Dvm & Reg. Compliance

**From:** Christine Yu, R.Ph.   
Regulatory Project Manager

**Company:** Discovery Laboratories, Inc.

Division of Pulmonary & Allergy Drug  
Products

**Fax number:** 215-340-3940

**Fax number:** 301-827-1271

**Phone number:** 215-340-4699

**Phone number:** 301-827-1051

**Subject:** Surfaxin IND 40,287  
Comments to submission 119 dated April 29, 2002

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:**

☐ YES

☒ NO

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We refer to your protocol KL4-IRDS-06 entitled, "A multinational, multicenter, randomized, controlled prophylaxis superiority trial of the safety and effectiveness of Surfaxin (lucinactant) compared to Exosurf (colfosceril palmitate) in the prevention of respiratory distress syndrome (RDS) in premature neonates," and to your submission dated April 29, 2002 (serial 119). Submission 119 included your responses to statistical comments regarding the data safety monitoring board (DSMB) standard operating procedures (SOP), the final Statistical Analysis Plan (SAP), and the draft SOP manual for the Death Adjudication Committee (DAC). We have reviewed the information submitted for protocol KL4-IRDS-06 and have the following comments.

Clinical Comments regarding the DAC SOP

1. For RDS-related mortality, please provide a clarification of the following.
  - How an infant who has a diagnosis of RDS and dies as a result of pulmonary hemorrhage will be classified.
  - How an infant who has a diagnosis of RDS and dies as a result of severe intracranial hemorrhage will be classified.
2. Two of the DAC members listed, (b) (4), have previously participated in Surfaxin clinical trials. Can they be regarded as truly independent?
3. We note the following.
  - Although the protocol speaks of the members of the DAC consisting of neonatologists and pediatric radiologists, only 1 pediatric radiologist is listed.
  - There is not much geographic variability among the committee members- might this influence the adjudication process?
  - We note that (b) (4) is no longer at the hospital listed.

Statistical comments regarding the final Statistical Analysis Plan (SAP)

4. Sample size re-estimation is planned if the observed number of events for the co-primary endpoints is lower than what is expected to maintain adequate power. Based on early information from the study, the recruitment period and/or the number of sites may be increased to obtain the pre-specified total number of events for both endpoints. If such re-estimation should occur, you have proposed use of one of two methods, one by Cui, Hung and Wang and one by Chen, DeMets and Lan. Both methods are statistically valid. If the sample size increase is not large, the two methods will probably render very similar results. Use of either method is acceptable. However, the method of Chen, DeMets and Lan may be more natural since it uses classical test statistics and does not need reweighting. If it is likely that the sample size increase needs to be large or that the re-estimated sample sizes differ based on the two methods, you may want to compare the performances of the two methods in terms of alpha and beta errors.

5. Regarding the primary efficacy analysis method, you stated that 'unless otherwise specified, efficacy analyses are performed on all randomized patients.' To avoid any potential ambiguity, we strongly recommend that the protocol clearly state that the primary efficacy analysis will be performed on all randomized patients.

Statistical comments regarding the DSMB SOP

6. It is well recognized that unblinding of individual patient data due to serious adverse events is sometimes necessary. However, the need to unblind the group indicator of a treatment assignment is not obvious unless a superior effect with Surfaxin is claimed at that interim analysis. We urge that you use the masked treatment identification (ID) whenever unblinding of individual patient data is necessary.
7. You have indicated that the O'Brien Fleming-type stopping function will be considered for this trial (Appendix I of submission 114 dated March 5, 2002). It is important that you submit the final (official) stopping rule as soon as possible and not to wait before the first formal assessment of unblinded data.

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/s/

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Christine Yu  
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CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 6, 2002

<b>To:</b> Christopher Schaber, Executive Vice President Drug Dvm & Reg. Compliance	<b>From:</b> Christine Yu, R.Ph. Regulatory Project Manager
<b>Company:</b> Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
<b>Fax number:</b> 215-340-3940	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-340-4699	<b>Phone number:</b> 301-827-1051

**Subject:** Statistical and clinical comments for Submission 103 dated January 7, 2002.

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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As a follow-up to the teleconference between the Division and Discovery Laboratories on March 4, 2002, the following are statistical and clinical comments to be incorporated into the Data Safety Monitoring Board Standard of Procedure (DSMB SOP) as soon as possible.

1. You have included the statistical analysis method in this amendment to be used for sample size re-estimation, i.e., 'Modification of sample size in group sequential clinical trials, Biometrics 55, 853-857, 1999.' Based on the mathematical argument, the proposed group sequential test may be valid when the time for consideration of sample size adjustment is not pre-specified prior to the first interim analysis, as long as it does not depend on the future data. The actual implementation of the method, however, relies on the proper operating procedure being clearly documented. To avoid potential operational bias from interim use of unblinded data to re-estimate the sample size, we strongly recommend that you pre-specify in the protocol the information time at which the sample size re-estimation is to be performed, in addition to the DSMB operating procedures to be submitted later as part of your standard operating procedure manual. We also strongly recommend that the sample size re-estimation be performed by an independent third party, such as the DSMB, to minimize the operational bias, if any. The conduct of the trial must be in accordance with the SOP.

If, however, you decide to use the conditional power approach for sample size re-estimation rather than pre-specification of a fixed information time, you are expected to submit an amendment to the IND at the time the sample size re-estimation takes place to address the concerns stated above.

2. We have noted your amendments to the first co-primary endpoint. It will **not** be acceptable to define Respiratory Distress Syndrome (RDS)-related mortality criteria in only that subset of patients who meet the protocol-defined RDS incidence at 24 hours of age. As discussed in our teleconference March 4, 2002, the definitions for cause-specific mortality and the Death Adjudication Committee SOP are critical concerns in the evaluation of this protocol. We have not received this information to date.

An RDS-related mortality disadvantage or no effect (an element of the second co-primary endpoint) may become a clinical review concern, even if Surfaxin showed a benefit on both incidence of RDS at 24 hours (first co-primary endpoint) and pulmonary air-leak at 7 days of age (an element of the second co-primary endpoint). The co-primary endpoint elements should be assessed to determine how each contributes to the overall combined result.

3. You state in this amendment that 'the final statistical model will include birth-weight, gender, and region in order to identify the independent effect of surfactant treatment.' However, you also state that 'by design, statistical models will include terms for surfactant treatment, birth-weight, center, and terms for the interaction of surfactant treatment with birth-weight and center, as well as terms for other important baseline variables that might be found to be significantly different between the two treatment

groups. Data from centers with fewer than 10 infants in either treatment group will be combined and analyzed as a single site.'

The statistical models described in the latter will be considered exploratory analyses only. The final statistical model will be the basis for the definitive primary efficacy evaluation.

Within the models, you have distinguished between 'center' and 'region.' Since the final statistical model is the basis for the definitive primary efficacy evaluation, you must clearly define the region a priori in the protocol, taking into account the design factors, such as, multi-nations.





Food and Drug Administration  
Rockville, MD 20857

IND 40,287

9/26/01  
IR

Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

Attention: Christopher J. Schaber  
Executive Vice President, Drug Development & Regulatory Compliance

Dear Mr. Schaber:

Please refer to your Investigational New Drug Application (IND) submitted August 4, 1992, and received August 6, 1992, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant).

Reference is made to your submissions dated February 20 and 26 and May 21, 2001. We have reviewed your new Protocol KL4-IRDS-06 entitled, "A Multinational, Multicenter, Randomized, Masked Controlled, Prophylaxis Superiority Trial of the Safety and Effectiveness of Surfaxin (lucinactant) compared to Exosurf (colfosceril palmitate) in the Prevention of Respiratory Distress Syndrome (RDS) in Premature Infants." This trial is safe to proceed with study enrollment at sites in the United States, however, we have provided the following comments addressing protocol deficiencies for your consideration and response.

We have also reviewed your Investigator Brochure and Protocol KL4-IRDS-02 entitled, "A Masked, Multicenter, Randomized, Controlled Trial Comparing the Safety and Effectiveness of Surfaxin (lucinactant) to Curosurf in the Prevention and Treatment of Respiratory Distress Syndrome (RDS) in premature neonates." This study is also safe to proceed with study enrollment at sites in the United States, however, we do NOT consider the trial design adequate to meet its stated efficacy objectives. Our comments pertaining to this study are provided to communicate the basis for our decision about this protocol design. We have also provided comments about other, less critical design deficiencies, since results of this study may be used in combination with Protocol KL-IRDS-06 to support Surfaxin safety.

Comments number 1-44 were previously forwarded to you in a facsimile transmission from the Division on August 23, 2001. Statistical comments, numbers 45-47, have **not** been previously forwarded.

**Protocol KL-4-IRDS-06**

1. A demonstration of efficacy for Surfaxin will depend on showing statistical superiority for **both** co-primary endpoints. The language specified for your second co-primary

endpoint, "...or either of the two components alone" should be clarified such that there is no question that "two components" refer only to RDS mortality through 14 days of age and/or air-leak through 7 days of age. We would like to clarify that the clinically relevant endpoint most important to the determination of Surfaxin efficacy is death due to RDS through day 14 and/or air leak through day 7.

2. Both the Data Monitoring Safety Board Standard of Procedure (DSMB SOP) and the Adjudication Committee Manual containing definitions of cause specific mortality should be clearly documented and submitted to the Agency prior to beginning the trial. Until we have seen these criteria outlined in the Adjudication Committee Manual, it is difficult for the Division to comment on this critical aspect of the protocol (co-primary endpoint #2). Rules for stopping the trial should be clearly specified in the DSMB SOP.
3. The DSMB should be evaluating the data masked to Surfaxin and Exosurf treatment assignment.
4. The protocol should specify clear and explicit guidelines for ventilation methods/modes, weaning, and extubation criteria. Incidence of RDS, a co-primary endpoint, is defined as the need for mechanical ventilation with an  $\text{FiO}_2$  requirement  $\geq 0.30$ , combined with a reticulogranular pattern on a chest radiograph. Since it is likely that the study cannot be perfectly masked, this endpoint as well as several secondary endpoints may be uninterpretable because introduction of bias could potentially affect the trial's results.
5. A 16-hour window for assessing RDS at 24 hours ( $\pm 8$  hours) is unacceptable and not concordant with the definition of "RDS at 24 hours" stated in Appendix 1 of the May 21, 2001, submission, which specifies assessment at 22-26 hours. Even a 4 hour window is wide, since assessment for the last dose of surfactant/sham is made at  $24 \pm 0.5$  hour of age. Further, the protocol does not specify whether assessment for RDS will be made prior to or after assessment of the need for a surfactant dose at 24 hours of age. Please amend your protocol to narrow the window for assessment of RDS at 24 hours that is concordant with assessment for the last dose of surfactant. Specify whether the assessment for RDS at 24 hours of age is made prior to, or subsequent to, the last dose of surfactant/sham.
6. Your estimated rates of mortality at some international sites where this trial is planned exceed the mortality rates in the sham/placebo group reported for the early surfactant trials conducted over 10 years ago. Since this is an event driven trial, significantly fewer than 1500 patients may be enrolled. This trial may be the only definitive trial to establish Surfaxin efficacy and comparative safety to an approved, labeled regimen of surfactant (Survanta). We strongly recommend, therefore, that the trial enroll a full 1500 patients and not stop prematurely unless stopping criteria pre-specified by the DSMB SOP are met.
7. Please clarify your rationale for not counting a patient who is treated for RDS, but who dies prior to 32 hours of age from causes other than RDS, as not having RDS. It is possible that if at 24 hours, the infant is on mechanical ventilation with an  $\text{FiO}_2 \geq 30\%$ , a chest x-ray will be obtained to confirm whether another dose of surfactant/sham should

be administered. Thus it is possible for an extremely premature infant to have both positive assessments of chest x-ray and FiO<sub>2</sub> at 24 hours of age, but die before 32 hours of age from non-RDS causes (e.g. congenital heart disease, overwhelming sepsis). In the current protocol, these infants will “lose” the diagnosis of having had RDS.

8. The protocol should clarify whether patients who die due to other causes through Day 7 will be counted as having had air leak. It is otherwise possible for an infant to have had RDS and air-leak at day 3 of life, but die at day 12 of life from other causes (e.g. perforated bowel) and be classified as having had no air-leak.
9. Although the primary objective of this study is to compare the efficacy and safety of Surfaxin with Exosurf, this protocol should also specify how the Survanta data will be assessed and reported for each of the efficacy and safety parameters.
10. The protocol should clearly state that the data will remain blinded until after 12 month follow-up assessments are all made, or alternatively clarify when finalization of the database occurs.
11. Exosurf dose administration does not conform to current labeling recommendations. Reflux of Exosurf has been associated with rapid drug administration and it is specifically labeled for slow administration. To improve safe conduct of this trial, the protocol should specify that reflux of surfactant may occur with rapid administration and offer recommendations for clinical intervention if this occurs.
12. The protocol does not exclude infants who require chest compressions or administration of epinephrine, bicarbonate, or fluid boluses in the delivery room, unlike Protocol KL4-IRDS-02, in which such patients are excluded. These infants are at higher risk of mortality and overall poor outcome and should therefore also be excluded in this protocol.
13. Inclusion criteria do not specify a lower bound for gestational age. The upper bound birth weight inclusion criteria of 1250 grams corresponds to less than the fifth percentile for a singleton 32 week gestation infant born in the United States in 1991 (Alexander, et al: A US reference for fetal growth. OB GYN 87:163, 1996). A small for gestational age infant may be expected to have more mature lung development than an infant born at the same birth weight and appropriate for gestational age. In your analysis of patient demographics, assessment of mean gestational age for each of the three, protocol-specified birthweight strata should be planned and compared across treatment arms. The protocol should also specify whether gestational age is preferentially measured by Ballard assessment or by best obstetrical estimate, based on last menstrual period (LMP) and/or fetal ultrasound.
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15. Different etiologies for air-leak should be tracked individually, and assessed for potential treatment differences.
16. Post-treatment acquired infection should be added to the list of co-morbidity endpoints associated with prematurity.
17. Neurodevelopmental outcomes assessed at 6 and 12 months are generally not considered "long-term" assessments in formerly premature infants. Long-term motor and cognitive assessments usually span years over an infant's life. Please delete "long-term" when describing neurodevelopmental assessments in this trial.
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19. Vigorous shaking of other surfactant preparations result in bubbles that make the surfactant difficult to remove from the vial. Is this an issue for Surfaxin?
20. Dose administration of all surfactants in this protocol specify turning the head to the left or right, in order to deliver the surfactant to the lung lobes on that side. The protocol should instead specify turning the head and body so that the dose is delivered to the dependant lung.
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22. Please correct an apparent protocol error in specifying a repeat fifth dose of any surfactant on page 28 of the May 21, 2001, submission. It is our understanding that no more than 4 doses of any surfactant will be administered.
23. The protocol should specify that dose associated adverse events are recorded with repeat dosing.
24. Protocol-specified analyses for safety assessment appear incomplete. Intra-dosing events of bradycardia, oxygen desaturation, changes in blood pressure, endotracheal tube (ETT) reflux of surfactant, etc., should be recorded on the case report form (CRF), and considered separately as intra-dosing adverse events (AEs). Intra-dosing AE differences among treatment groups during surfactant administration should be assessed and included in the Final Study Report.
25. Simple listing of concomitant medications is not adequate for the evaluation of concomitant medications. Differences among classes of medications between treatment groups should also be assessed.
26. All references to the ~~(b) (4)~~ (b) (4) f surfactant administration should be deleted from the protocol and investigator brochure.
27. Please submit sample case report forms, in English, and a list of study sites and investigators when they become available.

**Protocol KL-4-IRDS-02**

28. Informed consent for investigational sites within the United States should include a statement clarifying that any infant participating in this trial will NOT receive a surfactant approved specifically for prophylaxis of RDS. Informed consent should also identify that there ARE approved surfactants specifically available for prophylaxis of RDS.
29. The protocol design is inadequate to demonstrate its stated objectives for the following reasons:
  - a) This non-inferiority study (KL4-IRDS-02) is predicated on an unreliable effect size.
    - This **prophylaxis** study protocol is based on a single, open label **rescue (treatment)** study.
    - Medical practice change over the past decade may have impacted any of the efficacy endpoints specified in the Final Study Report of the historical Curosurf trial.
    - The combined study endpoint in this trial, survival without bronchopulmonary dysplasia (BPD) was not a specified efficacy endpoint in the original protocol for the Curosurf versus sham RDS treatment study.
    - BPD in the original protocol for the historical trial was not clearly defined. There were no defined x-ray criteria grading BPD, nor were there criteria to discontinue oxygen supplementation. Although a definition for BPD is contained in the current protocol, it cannot be identical to the historical Curosurf trial.
    - Investigators in the historical Curosurf trial were unblinded to treatment assignment. The individual interpreting chest x-rays or assessing need for oxygen supplementation was not identified in the protocol, and therefore, the potential for study bias has not been clarified.
  - b) An acceptable delta for a mortality endpoint in premature infants with RDS has not been established.
    - The current Curosurf prophylaxis protocol specifies preserving 50% of the effect size. However, this margin is based upon a margin accepted in thrombolytic trials that enrolled a different population, for a different indication, in which there was strong, **consistent** evidence of efficacy.
    - The proposed margin is not reasonable because we have only **one rescue** Curosurf versus sham/placebo demonstrating efficacy 1 [REDACTED] (b) (4)
30. This protocol does not assess both prevention and treatment strategies of Surfaxin effectiveness and safety. Amend your study objectives to reflect that this trial is solely a prevention trial in premature infants.
31. The superiority objective should be tested at either a two-sided 5% or a one-sided 2.5% level of significance.
32. This protocol does not specify mean airway pressure parameters or a statement of “maximal ventilator support,” or an upper bound for oxygen saturation in defining

- criteria for surfactant retreatment. These protocol deficiencies may result in inconsistent in use of supplemental oxygen and additional surfactant administration.
33. Appendix 1 of the February 26, 2001, submission defines inadequate parameters for requiring supplemental oxygen (oxygen to keep saturation  $\geq 92-95\%$ ). The upper bound of oxygen saturation should be clearly specified.
  34. In the high frequency ventilation weaning section, page 67 of the submission dated February 26, 2001, there is a typographical error which specifies reduction of FiO<sub>2</sub> to "below 3.0" before decreasing MAP. Please correct this error.
  35. Although the protocol refers the investigator to a definition of "days alive and off mechanical ventilation" in Appendix 1 of the February 26, 2001, submission, there is no such definition listed there. Please specify the missing definition.
  36. Appendix 5 of the February 26, 2001, submission lists nasal continuous positive airway pressure (CPAP) as a mode of ventilation in the Guidelines for Ventilation. Please clarify whether off mechanical ventilation refers to being off CPAP, conventional mechanical ventilation (CMV), and/or high frequency ventilation (HFV).
  37. Air leak is defined as pulmonary interstitial emphysema, pneumothorax, pneumomediastinum or pneumopericardium, as detected radiographically that are not resolved with presence of a chest tube. **All** air leak, irrespective of whether it is resolved with a chest tube, should be tracked and assessed.
  38. The body of the protocol should refer investigators to the Appendix guidelines for ventilatory management, since they are not also contained in the body of the protocol.
  39. As noted previously, criteria for extubation and parameters specifying the frequency of these assessments for possible should ideally be protocol specified.
  40. Post-dosing Section H (page 23) in the February 26, 2001, submission and sections of the Investigator Brochure (February 20, 2001, submission) refer to (b) (4) of surfactant treatment. All references to (b) (4) should be removed from both the protocol and the Investigator Brochure.
  41. The protocol should specify that all chest x-ray evaluations and follow-up evaluations of the infant are made by assessors masked to treatment assignment.
  42. The protocol should clearly state that the data will remain blinded until after 12 month follow-up assessments are all made or clarify when finalization of the database occurs.
  43. No assessment of anti-surfactant antibodies is included in this protocol. You state in both the Protocol Rationale and in the Investigator Brochure, that a potential advantage of a synthetic surfactant is non-antigenicity. Surfaxin contains a protein mimic with a chain of 21 amino acid residues (lysine and leucine) that may have immunogenic potential; therefore the potential for Surfaxin immunogenicity should be assessed in a subset of infants. (b) (4) should be deleted from both the protocol and the Investigator's Brochure.

44. Both Protocol KL4-IRDS-02 and KL4-IRDS-06 utilize administration regimens in the active treatment arms that are not approved. (Note that this may limit your ability to make any future comparative marketing claims for Surfaxin versus the other drugs and will impact on labeling.)

The following three comments pertain to **Protocol KL-4-IRDS-06** and have not been previously forwarded.

45. If the event rate for the two co-primary endpoints is lower than assumed, you plan to increase the sample size to power the study to at least 93% or higher. Please provide details of your statistical approach to sample size re-estimation for further review. Will the sample size increase be based on blinded data or the observed treatment difference? For the former case, an example would include the Gould and Shih approach (1992, Communications in Statistics, Theory, and Methods). For the latter case, useful approaches include Lan and Trost (1997, Proceedings of ASA Biopharmaceutical Section) and Ciu, Hung and Wang (1999, Biometrics).
46. As previously stated during our teleconference discussions of your Protocol Concept Study outline for Protocol LK-4-IRDS-06, a demonstration of Surfaxin superiority effectiveness requires that each of the co-primary efficacy endpoints show statistical significance at the 2-sided 0.05 level. The Agency believes that a superior Surfaxin effect may be demonstrated provided that each of the co-primary efficacy endpoints show statistical significance at the 2-sided 0.05 level.
47. Baseline variables included in the final statistical model need to be pre-specified (ICH E9).

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, call Ms. Christine Yu, Regulatory Project Manager, at 301-827-1051.

Sincerely,

*{See appended electronic signature page}*

Robert J. Meyer, M.D.

Director

Division of Pulmonary and Allergy Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research



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

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Robert Meyer  
9/26/01 04:59:09 PM





Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 16, 2001

**To:** Christopher Schaber  
Executive Vice President  
**Company:** Discovery Laboratories, Inc.

**Fax number:** 215-340-3940

**Phone number:** 215-340-4699

**From:** Christine Yu, R.Ph.  
Project Manager  
Division of Pulmonary and Allergy  
Drug Products

**Fax number:** 301-827-1271

**Phone number:** 301-827-1051

**Subject:** Clinical comments for protocols KL4-IRDS-02 and KL4-IRDS-06.

**Total no. of pages including cover:** 8

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.**

Reference is made to your submissions dated February 20, 2001, February 26, 2001, and May 21, 2001. We have reviewed your new Protocol KL4-IRDS-06 entitled, "A Multinational, Multicenter, Randomized, Masked Controlled, Prophylaxis Superiority Trial of the Safety and Effectiveness of Surfaxin (lucinactant) compared to Exosurf (colfosceril palmitate) in the Prevention of Respiratory Distress Syndrome (RDS) in Premature Infants." This trial is safe to proceed with study enrollment at sites in the United States, however, we have provided the following comments addressing protocol deficiencies for your consideration and response.

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Statistical comments will be forwarded at a later date.

#### **Protocol KL4-IRDS-06**

1. A demonstration of efficacy for Surfaxin will depend on showing statistical superiority for **both** co-primary endpoints. The language specified for your second co-primary endpoint, "...or either of the two components alone" should be clarified such that there is no question that "two components" refer only to RDS mortality through 14 days of age and/or air-leak through 7 days of age. We would like to clarify that the clinically relevant endpoint most important to the determination of Surfaxin efficacy is death due to RDS through day 14 and/or air leak through day 7.
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#### **Protocol KL-4-IRDS-02**

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41. The protocol should specify that all chest x-ray evaluations and follow-up evaluations of the infant are made by assessors masked to treatment assignment.
42. The protocol should clearly state that the data will remain blinded until after 12 month follow-up assessments are all made or clarify when finalization of the database occurs.
43. No assessment of anti-surfactant antibodies is included in this protocol. You state in both the Protocol Rationale and in the Investigator Brochure, that a potential advantage of a synthetic surfactant is non-antigenicity. Surfaxin contains a protein mimic with a chain of 21 amino acid residues (lysine and leucine) that may have immunogenic potential; therefore the potential for Surfaxin immunogenicity should be assessed in a subset of infants. (b) (4) should be deleted from both the protocol and the Investigator's Brochure.

44. Both Protocol KL4-IRDS-02 and KL4-IRDS-06 utilize administration regimens in the active treatment arms that are not approved. (Note that this may limit your ability to make any future comparative marketing claims for Surfaxin versus the other drugs and will impact on labeling.)





Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 22, 2001

<b>To:</b> Christopher J. Schaber	<b>From:</b> Christine Yu
<b>Company:</b> Discovery Laboratories, Inc.	Division of Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 215-340-4699	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-340-3940	<b>Phone number:</b> 301-827-1051

**Subject:** Minutes of teleconference March 22, 2001

**Total no. of pages including cover:** 4

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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error, please notify us immediately by telephone at (301) 827-1050. Thank you.**

## MEMORANDUM OF TELECON

DATE: February 22, 2001

APPLICATION: IND 40,287 Surfaxin (lucinactant)

BETWEEN: Discovery Laboratories, Inc.

Name: Robert Capetola, President and CEO  
Christopher Schaber, Executive VP, Drug Development and  
Regulatory Compliance  
Robert Segal, Vice President, Clinical Research

AND Division of Pulmonary and Allergy Drug Products, HFD-570

Name: Robert Meyer, Division Director  
Christine Yu, Regulatory Project Manager

SUBJECT: Surfaxin Press

Background: The press gained access to information presented during CDER Scientific Rounds regarding a proposed placebo-controlled RDS (respiratory distress syndrome) trial with Surfaxin in Latin America. The sponsor acknowledged to the press that they are considering a trial as such and added that Surfaxin will not carry the risk of BSE (bovine spongiform encephalopathy) that other animal derived surfactants may carry. The Center Director requested that the Division speak to the sponsor regarding not raising the BSE issue inappropriately during sponsor interactions with the press.

Telecon: Discovery stated that the press has knowledge of propriety information regarding Surfaxin. Sydney Wolfe (from Public Citizen) has sent a letter to the Secretary of Health & Human Services which includes information about the proposed trial and material presented at Scientific Rounds.

Dr. Meyer stated that the information presented during Scientific Rounds were to educate and to allow for ethical discussion only within the FDA. The specifics about Surfaxin were masked during the presentation and procedures to safeguard propriety information were followed.

Dr. Meyer stated that the Center Director, Dr. Janet Woodcock, requested that Discovery Laboratories not raise the BSE issue inappropriately during interactions with the press.

## MEMORANDUM OF TELECON

DATE: December 18, 2000

APPLICATION: IND 40,287

BETWEEN: Discovery Laboratories, Inc.

Name: Timothy Gregory, Senior Director, Clinical Development & Administration

Lisa Mastroianni, Director, Clinical Research

(b) (4)

Adam Rumage, Regulatory & Quality Associate

Christopher Schaber, Executive Vice President, Drug Development and Regulatory Compliance

Robert Segal, Vice President, Clinical Research

Huei Tsai, Vice President, Biometrics

AND from Division of Pulmonary and Allergy Drug Products, HFD-570

Name: Debra Birenbaum, Medical Officer

Lisa Kammerman, Biometrics Team Leader

Marianne Mann, Deputy Director

Robert Meyer, Division Director

Sue-Jane Wang, Senior Mathematical Statistician

Steve Wilson, Biometrics Team Leader

Christine Yu, Project Manager

SUBJECT: Minutes of teleconference December 18, 2000  
Surfaxin RDS Latin America protocol

Summary of activity to date:

August 9, 2000 Teleconference with the Division, Discovery outlined plans to conduct a placebo-controlled Surfaxin RDS trial in Latin America.

November 7, 2000 Representatives of various Offices within the Agency held an internal meeting and discussed Discovery's plans for the trial.

November 13, 2000 Discovery submitted protocol KL4-IRDS-04, "*A Multicenter, Randomized, Masked, Placebo-Controlled Trial Comparing the Safety and Effectiveness of Surfaxin to Standard of Care in the Treatment of Respiratory Distress Syndrome (RDS) in Premature Neonates.*"

- November 27, 2000 Division sent letter to Discovery expressing concerns regarding ethicality of the proposed trial and the applicability of such data to the U.S. population and recommended further discussion before initiation of the trial.
- December 14, 2000 Discovery faxed justification for proposed trial in preparation for this teleconference.

The Division opened the teleconference by informing the sponsor that an Agency level meeting will be held, at which the Division would like to present Discovery's complete rationale and point of view for this protocol. The Division requested as much detail and concrete facts as possible that could be provided from Discovery, to address the remaining ethical and data applicability concerns. Division concerns are represented in Italics and are followed by Discovery's response and discussion in normal font.

1. *Provide more detail about Discovery's concept that Surfaxin would be "cost-effective." Does Discovery have projected costs for Surfaxin as compared to costs for current products out on the market? Some actual numbers would be helpful and would provide concrete data for review.*

Discovery responded that the animal-derived surfactants are \$400-\$500 per vial, and most babies need 2-3 vials. In contrast, 75% of babies needed only 1 vial of Surfaxin in the phase 1-2 clinical trials performed to date. Other surfactants are marketed at the same price or higher outside of the U.S. Discovery does not have the estimated price currently, but Surfaxin would be significantly less. Discovery has committed to work with the governments of Latin America host countries, to assure that Surfaxin would be accessible in those countries following local approval.

2. *Provide more detail on how Discovery will make Surfaxin "available at a reduced cost to the participating countries in Latin America following local approval." Specify projected Surfaxin cost to the host country and the length of commitment to that country. Provide copies of written agreements with host countries, which specify that post-approval Surfaxin costs would not limit Surfaxin accessibility in host country regions which cannot afford the cost of currently approved surfactants.*

Discovery gave the following time-frames for prices.

◆  
◆  
◆

(b) (4)

Discovery also stated that the training that they will be providing to the health professionals during the clinical trial is another added benefit which will effect all babies in that region.

*Specify what ancillary medical support you will be providing to assure comparable standard of care between Latin American infants and U.S. infants, e.g., ventilators, equipment and qualified medical personnel to perform echocardiograms and head ultrasounds, medications and qualified medical personnel to treat other co-morbidities associated with prematurity.*

Ancillary services provided will vary from center to center, but the trial will be conducted under Good Clinical Practices (GCPs). Discovery representatives have visited many of the centers, and it is clear that standards are different from the U.S. and that there is much variability in equipment status.

The Division agreed that training provided by Discovery should benefit infants in both arms of the trial. However, it is not clear that this training period will be adequate to address significant standard of care differences that may impact both mortality and morbidity, and therefore, data applicability concerns remain.

The Division added that in spite of best efforts surfactant trials are difficult to perfectly blind. Investigators may be able to infer which trial arm the infant has been randomized to from observed endotracheal tube (ETT) reflux and changes in oxygenation parameters after dosing administration. Introduction of investigator bias might result in unequal escalation of care opportunity for infants in both trial arms. This potential for bias may affect the trial endpoints and may alter a presumed equal benefit to risk ratio for each randomized infant at trial enrollment.

Discovery replied that placebo-controlled trials in the past were not blinded, but they will be masking this trial. The Surfaxin syringes will be opaque, and although ETT Surfaxin reflux may be apparent, protocol procedure will separate those preparing the doses from those who will be administering the doses, from those who will care for the infant after the dose has been given.

3. *Differences in perinatal care between the host countries and the U.S. may be reflected in the effect size seen in your Latin American trial. Current plans to conduct a single, two arm trial, without an active comparator arm (such as an approved, animal-derived surfactant) limit trial interpretability for data application to the U.S. population.*

*Adding an active comparator arm would improve data interpretability and increase trial ethicality by increasing the probability to 2 out of 3 that a baby will receive a surfactant. The active comparator arm would serve as an anchor to interpret effect size compared to the U.S., where mortality is about 12-14%.*

Discovery responded that adding the third arm would delay the trial at the cost of babies' lives, which is an ethical concern, and would not add benefit to the trial. Furthermore, the trial will not be powered sufficiently to show a difference. On the other hand, (b) (4)

The Division stated that the number of patients that would need to be in the third arm still needs to be determined. In part, this decision would be based on information submitted about the EU trial. Discovery can proceed with the planned 2-arm trial for approval in Latin America, providing drug without delay to ill Latin American infants. However, the data may be meaningless to the U.S. population. The recommendations given, therefore, are the conditions for U.S. approval, should conduct of this placebo-controlled trial be considered ethical.

4. *The results of a recent trial of ALEC (pumactant) versus Curosurf (poractant alfa) highlight the need for caution when assessing how many trials, and what kind of trials, may be necessary for new surfactant approval. The Agency needs to be assured that we are not approving an inferior product, especially when benefit from synthetic surfactants may be questionable.*

Discovery stated that Surfaxin has characteristics that make it different from other synthetic surfactants.

The Division noted that Infasurf was approved following demonstrated superiority over Exosurf. The Division requested that Discovery submit a justification for not doing a superiority trial against Exosurf in Latin America.

Discovery responded that the discussion of why physicians would not enroll infants into a trial where Exosurf was a potential treatment has been held before with the Division.

The Division clarified that in previous discussions regarding an Exosurf superiority trial, enrollment difficulties and ethical concerns were posed by U.S. physicians. If Latin American physicians agree to a placebo-controlled trial, a superiority trial against Exosurf should also be feasible.

#### **Information requested from Discovery**

The Division requested that the following information be submitted no later than January 24, 2000. The internal Agency level meeting will not be scheduled unless all information is received.

1. Provide specifics and details how Surfaxin will be "cost effective," the duration of agreements with the host countries, and copies of written agreements, if any.
2. Provide details how standard of care will be raised in the study sites.
3. Submit EU protocol, as currently available.
4. Address in detail, Discovery's rationale for adding or not adding a third arm.
5. Most importantly, provide Discovery's rationale for not conducting a superiority trial against Exosurf in Latin America.

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Christine Yu, R.Ph.  
Project Manger

/s/

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Christine Yu  
1/11/01 04:26:39 PM  
CSO





Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 22, 2001

<b>To:</b> Christopher J. Schaber	<b>From:</b> Christine Yu
<b>Company:</b> Discovery Laboratories, Inc.	Division of Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 215-340-4699	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-340-3940	<b>Phone number:</b> 301-827-1051
<b>Subject:</b> Minutes of teleconference March 29, 2001	

**Total no. of pages including cover:** 3

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## MEMORANDUM OF TELECONFERENCE

DATE: March 22, 2001  
TIME: 3:00 – 4:00 PM  
APPLICATION: IND 40,287 Surfaxin (lucinactant)

BETWEEN: Discovery Laboratories, Inc. (unless noted)

Name: Robert J. Capetola, President/CEO  
Timothy Gregory, Senior Director, Clinical Development & Administration  
(b) (4)  
Adam Rumage, Senior Regulatory & Quality Associate  
Christopher J. Schaber, Executive Vice President, Drug Development & Regulatory Compliance  
Robert Segal, Vice President, Clinical Research & New Drug Evaluation  
Huei Tsai, Vice President, Biometrics  
Thomas Wiswell, MAS Clinical Advisor

AND Division of Pulmonary & Allergy Drug Products (unless noted)

Name: Debra Birenbaum, Medical Officer  
John Jenkins, Director, Office of Drug Evaluation-II  
Marianne Mann, Deputy Director  
Robert Meyer, Division Director  
Sue-Jane Wang, Senior Mathematical Statistician  
Christine Yu, Regulatory Project Manager

### Background

A face to face meeting was held on March 12, 2001, between the Division and Discovery Laboratories to discuss their "Alternate Surfaxin prophylaxis vs. Survanta rescue superiority trial design" which was faxed to the Division March 8, 2001 (serial 084). On March 14, 2001, Discovery faxed to the Division their proposal of the 3-arm trial design discussed during the March 12<sup>th</sup> meeting. The following comments were faxed to Discovery on March 19, 2001.

- ◆ Although the overall design appears feasible, the primary endpoint of occurrence of (or time to) respiratory distress syndrome (RDS) is inadequate to support a prophylaxis indication for the development of RDS in premature infants.
- ◆ We are not comfortable defining a directionally concordant trend for secondary endpoints that, used in combination with your primary endpoint, would serve to support Surfaxin registration for this indication.

Discovery requested a teleconference.

### Teleconference

Discovery asked for clarification about the Division's perspective about the proposed trial, because it was different from the perspective discussed at the March 12<sup>th</sup> meeting. Discovery added that they

were still receiving much pressure from the media regarding the status of the proposed placebo-controlled Latin America trial.

The Division responded that at the March 12<sup>th</sup> meeting, while the Division stated that the proposed trial design was a potential path forward, there was not complete resolution about the trial design or appropriate endpoints.

The Division stated that the incidence of RDS cannot be considered a clinically relevant primary endpoint that will stand on its own without other primary clinically relevant endpoints. The Division added that they were not comfortable defining a sufficient directional concordance of supporting clinically relevant endpoints, short of statistical significance in those endpoints.

(b) (4), referencing the Academy of Pediatrics, stated, "respiratory failure is secondary to the lack of surfactants." He stated that incidence of RDS is a clinically relevant endpoint, having high associations with mortality and morbidity, higher than bronchopulmonary dysplasia (BPD) and patent ductus arteriosus (PDA).

Dr. Wiswell stated that the secondary morbidities should follow incidence of RDS.

The Division responded that incidence of RDS is not a proven surrogate for mortality or RDS morbidities. In fact, incidence of RDS has not always tracked directionally with these other clinically relevant endpoints in historical surfactant trials. Further, incidence of RDS is defined by x-ray and/or oxygenation parameters, which, while reasonable measures of short term benefit, do not correlate with ultimate direct clinical benefit to the infant. In Dr. Roger Sol's meta-analyses, mortality and co-morbidities were selected as meaningful endpoints, not incidence of RDS. If incidence of RDS was a proven clinically relevant endpoint, one would have expected that it, too, would have been used in those analyses.

The Division noted an additional concern about using incidence of RDS as the primary endpoint. The investigators in the trial would, in actuality, likely be unblinded to treatment group. This may result in an investigator bias toward diagnosing of RDS more quickly in the rescue arm of the trial, so that rescue therapy could be administered.

Discovery stated that they expected that the proposed placebo-controlled trial in Latin America would have shown the differences between Surfaxin treatment and placebo treatment with a rescue regimen. Unfortunately, because of the leak to the press regarding the trial design, the trial was no longer an option.

The Division responded that they have already acknowledged its regret that there was an inappropriate leak of information to the press regarding the protocol, but the fact that the leak happened does not lower the Agency standards that drugs must be proven safe and effective. Additionally, the Division noted they had not yet determined whether the proposed placebo-controlled trial in Latin America was ethical. If Discovery chose to take the risk and proceed with the proposed placebo-controlled trial under the IND, they risked being placed on clinical hold.

The Division further stated that incidence of RDS as a single primary endpoint is not adequate to gain approval, even if Discovery goes ahead with the trial and wins on this endpoint. If a composite

endpoint is used, the sponsor must be careful that the composite endpoint is not "driven" by incidence of RDS.

Discovery asked if the addition of the Survanta reference arm coupled with trial results from the European Union (EU), would provide sufficient data to meet regulatory approval.

The Division responded that the Agency cannot predict the results of the trial, but with the design of the EU trial, interpretation of the data would be difficult. They added that Discovery has entered into an area of medicine in which it is difficult to perform a clinical trial in the year 2001. The sponsor of a new surfactant must be able to show efficacy in comparison to available surfactants. The Division suggested that a Surfaxin trial showing superiority over Exosurf might be reconsidered. The Division again expressed its commitment in working with Discovery in finding alternative paths forward.

Submitted by,

Christine Yu, R.Ph.  
Regulatory Project Manager

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/s/

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Christine Yu  
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CSO



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Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 22, 2001

<b>To:</b> Christopher J. Schaber	<b>From:</b> Christine Yu
<b>Company:</b> Discovery Laboratories, Inc.	Division of Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 215-340-4699	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-340-3940	<b>Phone number:</b> 301-827-1051
<b>Subject:</b> Minutes of teleconference April 4, 2001	

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## MEMORANDUM OF TELECONFERENCE

DATE: March 29, 2001  
TIME: 1:00 – 2:00 PM  
APPLICATION: IND 40,287 Surfaxin (lucinactant)

BETWEEN: Discovery Laboratories, Inc.(unless noted)

Name: Robert J. Capetola, President/CEO  
Timothy Gregory, Senior Director, Clinical Development & Administration  
Carlos Guardia, Medical Director, Latin America  
Lisa Mastroianni, Sr. Director, Clinical Research

(b) (4)

Adam Rumage, Senior Regulatory & Quality Associate  
Christopher J. Schaber, Executive Vice President, Drug Development & Regulatory Compliance  
Robert Segal, Vice President, Clinical Research & New Drug Evaluation  
Huei Tsai, Vice President, Biometrics  
Thomas Wiswell, MAS Clinical Advisor

AND Division of Pulmonary & Allergy Drug Products (unless noted)

Name: Debra Birenbaum, Medical Officer  
John Jenkins, Office Director, ODE-II  
Robert Meyer, Division Director  
S. Edward Nevius, Biometrics II, Division Director  
Sue-Jane Wang, Senior Mathematical Statistician  
Christine Yu, Regulatory Project Manager

### Background

A teleconference was held on March 22, 2001, between the Division and Discovery Laboratories regarding concerns raised by the Division regarding a proposed trial entitled, "A multinational, three-arm, masked, controlled Surfaxin prophylaxis superiority trial with Surfaxin or Survanta rescue." As follow-up to the March 22<sup>nd</sup> teleconference, Discovery faxed a revised trial design, "A multinational, masked, randomized, Surfaxin versus Exosurf prophylaxis superiority trial" on March 26, 2001, and requested discussion with the Division as soon as possible.

### Teleconference

The Division stated that the current proposal is a good design, but the major concerns continue to be a single primary endpoint with questionable clinical relevance in a pivotal study, and the absence of a natural surfactant reference arm in a multinational trial. Discovery's proposal to place a  $p=0.3$  for an air-leak endpoint does not compensate for these deficiencies.

The Division proposed a single large 3-arm international study, to include Surfaxin, Exosurf and a natural surfactant active comparator, which may alone be enough to support the NDA. The comparator arm helps address the applicability of data to the U.S. population. The natural surfactant active comparator arm will provide reference by which to roughly compare the efficacy of Surfaxin.

The primary comparison would be between Surfaxin and Exosurf; however, the sponsor needs to choose a clinically relevant endpoint as primary or co-primary, with a  $p \leq 0.05$ . The Division stated that they realize that the sample size might increase significantly, depending on the chosen endpoint.

Discussion ensued regarding clinically relevant endpoints and acceptable p-values with reasonable sample sizes. The Division stated that air leak and RDS-related mortality may be considered clinically relevant endpoints, in addition to overall mortality. From a clinician's point of view, the most relevant endpoint would likely be survival without chronic lung disease at 36-week post conceptual age, but this may be extremely difficult to show. Thus, it is not being recommended for this trial.

Additionally, the Division noted that the proposed trial included infants 750-1250 grams at birth. Because the use of surfactants in infants less than 700 grams is not infrequent and because there is usage reported in the Vermont Oxford Database, inclusion of some infants less than 700 grams may be considered for the trial. Surfaxin would be one of the few surfactants studied in infants less than 700 grams.

Discovery noted that in the Infasurf/Exosurf trial 3 co-primary endpoints were used, and Infasurf won in 2 out of the 3 endpoints.

The Division stated that if a co-primary endpoint is used, each endpoint must separately meet  $p \leq 0.05$ .

The Division proposed the following co-primary endpoint for a 3-arm prophylaxis trial with a 2:2:1 ratio for Surfaxin: Exosurf: natural surfactant active comparator.

1. Incidence of RDS, and
2. RDS-related mortality through 14 days and/or air-leak through 7 days of age (a composite).

The trial design and proposed co-primary endpoints were acceptable to Discovery. Discovery agreed to fax to the Division their understanding of today's agreements.

The Division commented that Discovery has the option of conducting one trial with a bigger sample size, instead of also conducting a trial in the E.U. that might not provide any useful data. But, Discovery must balance the risk to drug development and corporate finances in relying on a single study.

Submitted by,



Christine Yu, R.Ph.  
Regulatory Project Manager





Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 22, 2001

<b>To:</b> Christopher J. Schaber	<b>From:</b> Christine Yu
<b>Company:</b> Discovery Laboratories, Inc.	Division of Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 215-340-4699	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-340-3940	<b>Phone number:</b> 301-827-1051

**Subject:** Minutes of meeting March 12, 2001

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IND 40,287

Date: September 11, 1995

Drug Product: KL4 Surfactant

Sponsor: Charles Cochrane, M.D., The Scripps Research Institute

Manufacturer of Test Article:

(b) (4)

Contract Research Organization:

(b) (4)

Attendees:

FDA Martin Himmel, Miriam Pina, Steve Wilson, Tony Koutsoukos, Y. Soo Choi,  
Chong Ho Kim, Linda Ng, Ramana Sista, Betty Kuzmik, John McCormick

Industry Charles Cochrane (The Scripps Research Institute), Susan Revak (The Scripps  
Research Institute),

(b) (4)

(b) (4)

## BACKGROUND

IND #40,287 was submitted to the Division in August 1992. A request for an End-of-Phase 2 meeting was made by Dr. Cochrane in April 1995 and a meeting packet was sent in mid-May. This meeting was held to discuss the proposed study design for Protocol KL4-IRDS-001, "A Masked, Multicenter, Randomized, Controlled Trial Comparing the Effectiveness and Safety of KL4-Surfactant and Survanta in Low Birth Weight Neonates with Respiratory Distress Syndrome (RDS)" as well as any other issues pertinent to an NDA submission.

## INTRODUCTION

Dr. Cochrane presented background information on KL4 Surfactant, an entirely synthetic, peptide-containing surfactant.

## CHEMISTRY

Dr. Kim reminded the group that the CMC information requested in the letter dated Feb 9, 1995 needs to be addressed. In addition, he pointed out that the purity of KL4 was listed as > 95% in the (b) (4), but later on, in vol 3.1, it was listed as 75%. He asked that this discrepancy be corrected. Other requests and recommendations made to the sponsor are as follows.

The material balance should be investigated and reported. Impurities (individual and total) specifications and methods should be established.

Photostability studies should be performed per ICH proposal (100 ft candles may not be appropriate).

Equivalency and stability of the products manufactured at the 3 different sites should be established.

For the drug product specifications and methods, a more quantitative approach for color,

identification, sterility, impurities (total and individual), and particle size distribution should be included.

A copy of the Agency's guidelines entitled, "Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances" (published Nov 1994) was given to the sponsor.

(b) (4) stated that some of these issues have already been addressed in their recent submission that the Division has not yet received. As requested by them, Drs. Kim and Ng agreed to a separate meeting in the future with a focus on the pending CMC issues.

#### PHARMACOLOGY/TOXICOLOGY

For NDA approval, Dr. Choi stated that 2 newborn studies with 7 day dosing in 2 different species are needed. The sponsor voiced concern about the fragility of premature animals. They questioned the need to use newborns (rather than adults) as well as the need to conduct studies for a full 7 days of dosing when it is much longer than the dosing period for the indicated patient population. Dr. Himmel responded by saying that collection of preclinical data for longer periods than the actual treatment duration is useful in enhancing the ability to determine toxicity. Dr. Choi stated that 3 - 4 week old newborns (or even older if the sponsors wish and it is discussed with this Division first) will be allowed to be used for the studies. Use of premature animals is not necessary.

Suggested second species are rabbits, rats, and ferrets.

#### CLINICAL

The following points were made by Dr. Pina.

1. The sponsor needs to choose a better (more suitable) active control than Survanta in their current proposed protocol.
2. When that is chosen, then equivalency needs to be defined in a way that is acceptable. In their current trial, the definition of equivalency is not acceptable.
3. In a pivotal study, reproducibility must be shown with the particular chosen endpoints. Therefore, 2 studies are needed. One trial might be acceptable but only if KL4 showed overwhelmingly greater superiority with the first trial and only after review and agreement by the Division.

This was explained in the following manner. To do an equivalency trial, the chosen active control must have previously demonstrated, in a consistent manner, statistically significant superiority over placebo in a similar patient population and on the same endpoints as those in the equivalency trial. In 2 previous rescue trials with Survanta using endpoints of BPD or RDS related death at 28 days (from package insert), Survanta beat placebo in only 1 of them with an absolute difference of 20%. In a trial comparing KL4 with Survanta, as proposed by the sponsor, the problem is that there would be no way to know if Survanta would beat placebo every time, so there would also be no way to know with certainty if KL4 was any better than placebo. In a comparative trial without a placebo, the burden of proof is on the sponsor that the comparator is better than placebo.

Dr. Himmel suggested that one of their options is to redesign a trial to show that KL4 is better than one of the other surfactants currently marketed. Dr. Cochrane and (b) (4) discussed comparing KL4 to Exosurf but according to them, after publication of results from a large NIH study where Survanta was found to be preferable to Exosurf by a significant margin, most large clinical trial

centers have switched to Survanta. In fact, centers are no longer even using Exosurf at all in low birth weight babies. For that reason as well as the legal implication (attorneys know outcomes of trials before many physicians do), (b) (4) stated that studies comparing KL4 to Exosurf would be very difficult to conduct in this country.

According to Dr. Cochrane and (b) (4), centers would prefer using KL4 over Exosurf even though KL4 is still experimental. They like the idea of using a product that incorporates peptides, has no health risks compared to animal derived surfactants, and has the advantage of cost and simplicity. It was also pointed out that it takes 30 min to 1 hr just to reconstitute Exosurf or to warm Survanta which is not needed with KL4.

Dr. Cochrane and (b) (4) expressed distraught over the seemingly impossible task ahead of them. Dr. Himmel voiced his understanding of the difficulty in conducting clinical trials now when use of placebos would be considered unethical as compared to 5 - 10 years ago when placebos could be used.

Further discussion ensued about ideas for possible study endpoints. Endpoints of death and BPD are not absolutely essential. There can be a variation but air leaks and IVH were not considered adequate by the Division. Endpoints for KL4 would need to be tied to the endpoints used with Survanta (similar endpoint with similar patient population). If showing superiority, then the endpoints would not need to be tied to Survanta.

RDS death was suggested but (b) (4) felt that the chances of using that are very low. In babies weighing 600 - 800 Grams with health problems that are multifactorial in etiology, cause of death due to RDS is hard to differentiate from overall death. Putting together a protocol with a mortality linked endpoint backed up with Survanta data on that endpoint for an equivalency trial was thought by (b) (4) to be too complicated and difficult.

Number of doses to cure RDS would be acceptable as a secondary endpoint only, according to Dr. Himmel.

Incidence of RDS as a primary endpoint may be a reasonable endpoint for a prophylaxis study. Dr. Cochrane and (b) (4) were encouraged to put together some proposals after which the Division would provide additional feedback.

Guidelines for equivalency were requested by (b) (4) but they were told that there are is no standard definition. Each protocol is evaluated individually based on the type of endpoints chosen to decide what would be an acceptable preservation of the effect size of the active control vs. placebo.

For an equivalency trial, a one sided 95% confidence interval is considered acceptable.

For a prophylaxis study, (b) (4) had questions about the definitions of RDS and prophylactic treatment since they are defined so variably (not uniformly across the country) and that makes it difficult. It was pointed out that they could define them in a way that was consistent across the centers conducting their studies. These definitions, though, should also be consistent with the definitions used in the active control trials.

Dr. Cochrane voiced his distraught at the possibility of losing the support of (b) (4), the CRO, and subsequently the opportunity to use KL4 for IRDS.

Again, their options were repeated. They were encouraged to check clinical trials on Survanta here in the U.S. as well as in other countries, to find centers still using Exosurf, and to change

their protocol rescue study to prophylaxis studies. No other suggestions could be provided at the time of the meeting but the group was told that we would be willing to discuss these issues with them in the future.

*Betty Kuzmik*

Betty Kuzmik, Project Manager

cc:

Original IND

HFD-155/Division File

HFD-155/Himmel/9-12-95

HFD-155/Pina/9-12-95

HFD-155/WilsonS

HFD-155/Koutsoukos/9-12-95

HFD-155/Sista/9-12-95

HFD-155/Poochikian

HFD-155/Kim/9-12-95 Chung-Ho

HFD-155/Ng/9-12-95

HFD-155/Choi/9-12-95

HFD-155/Sun

HFD-155/Schumaker/9-12-95

HFD-155/Kuzmik

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## MEMORANDUM OF TELECONFERENCE

DATE: April 4, 2001

APPLICATION: IND 40,287 Surfaxin (lucinactant)

BETWEEN: Discovery Laboratories, Inc.

Name: Robert J. Capetola, President/CEO  
Timothy Gregory, Senior Director, Clinical Development & Administration  
Brian Marcy, Clinical Project Manager  
Lisa Mastroianni, Sr. Director, Clinical Research  
Adam Ramage, Senior Regulatory & Quality Associate

AND Division of Pulmonary & Allergy Drug Products

Name: Debra Birenbaum, Medical Officer  
Marianne Mann, Deputy Director  
Sue-Jane Wang, Senior Mathematical Statistician  
Christine Yu, Regulatory Project Manager

### Background

During a previous teleconference on March 29, 2001, Discovery Laboratories and the Division reached a tentative agreement on trial design and endpoints for a Surfaxin superiority trial against Exosurf. On March 30, 2001, Discovery faxed to the Division their understanding of what was discussed during the teleconference in a protocol entitled, "A multinational, masked, randomized, Surfaxin versus Exosurf prophylaxis superiority trial with Survanta as a reference arm." The Division agreed to convey agreement or disagreement with the proposed protocol and endpoints to the sponsor as soon as feasible.

### Teleconference

The Division initiated the telecon by informing Discovery that Dr. Peter Lurie from Public Citizen had called again, asking questions regarding Discovery's most recent press release on their website. The Division stated that Dr. Lurie was informed that the confidential FDA information obtained inappropriately by Public Citizen was inaccurate and incomplete. In addition, Dr. Lurie was also told that many trial designs had been under discussion between Discovery and the Division.

Discovery stated that Dr. Lurie had called them also and that they had replied to Dr. Lurie very similarly.

The Division stated that Discovery's proposal conforms to the general agreements made during the March 29<sup>th</sup> teleconference. There were some remaining clinical and statistical concerns that could be addressed when the full protocol is received.

The following were clinical concerns that the Division wanted to convey to Discovery before the full protocol is submitted.



1. Pre-specify the definition of “respiratory distress syndrome (RDS) related mortality at 14 days” [for circumstances where it might be confounded by chronic lung disease (CLD)-related mortality, or any other cause of mortality].

2. Pre-specify the death adjudication committee.

Discovery has planned an adjudication committee and will add it to the protocol.

3. Secondary endpoints should include all-cause mortality at 14-days, RDS mortality at 14-days, and incidence of air-leak, all as separate endpoints.

Discovery agreed.

4. Provide random stratification by birth weight groups of 600-800 grams, 801-1000 grams, and 1001-1250 grams, since there may be important differences in infant maturity, which may effect study endpoints. The proposed 2 birth weight strata may be insufficient and are not advised. Furthermore, if Discovery chooses to stratify by age or weight, the details of stratification need to be specified in the protocol.

Discovery will consider this recommendation.

5. Be specific in the case report form (CRF), tracking antenatal steroid use as complete, incomplete, or no course of therapy.
6. Specify rescue therapy provision parameters for use of post-natal steroids and high frequency ventilation. Specifying such parameters may decrease noise in the study.
7. A full complement of 1500 infants must be enrolled for the trial. The trial should not stop based on number of events, even if incidences are met before the trial has enrolled 1500 infants.

Discovery will discuss this recommendation. A caveat to this is if the Data Safety Monitoring Board (DSMB) stops the trial for all-cause mortality (no look on Discovery's end).

On a further note, the Division stated that although a DSMB is involved with monitoring of mortality related endpoints, no statistical penalty is included in the current concept sheet. Discovery needs to prespecify what rule they will follow for the interim analysis.

Discovery asked if the trial could win just on one of the co-primary endpoints, having a p-value less than 0.05.

The Division responded that both co-primary efficacy endpoints need to make it at the 2-sided 0.05 level.

The Division noted that a prophylaxis trial will only support a prophylaxis indication and asked if Discovery is still proceeding with the non-inferiority trial in the European Union.

Discovery replied that the European study is still being planned with a trial against Curosurf.  
Discovery thanked the Division for the comments and stated that they will submit the full protocol as soon as it is ready.

Submitted by,

A handwritten signature in black ink, appearing to read 'C. Yu', written over the printed name.

Christine Yu, R.Ph.

Regulatory Project Manager





Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 19, 2001

<b>To:</b> Christopher J. Schaber	<b>From:</b> Christine Yu
<b>Company:</b> Discovery Laboratories, Inc.	Division of Division of Pulmonary and Allergy Drug Products
<b>Fax number:</b> 215-340-3940	<b>Fax number:</b> 301-827-1271
<b>Phone number:</b> 215-340-4699	<b>Phone number:</b> 301-827-1051
<b>Subject:</b> Comments for Prophylaxis Superiority trial with Surfaxin or Survanta Rescue	

**Total no. of pages including cover:** 2

**Comments:**

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**Document to be mailed:** ☐ YES ☒ NO

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Reference is made to your March 14, 2001, fax, which includes an outline protocol entitled, "A multinational, three-arm, masked, controlled Surfaxin prophylaxis superiority trial with Surfaxin or Survanta rescue." In your fax, you define your primary endpoint as, "time to development of RDS requiring surfactant rescue," with directional concordance of all-cause mortality. After review and discussion at the Division and Office level, we have determined the following:

1. Although the overall design appears feasible, the primary endpoint of occurrence of (or time to) RDS is inadequate to support a prophylaxis Surfaxin indication for premature infants at risk for development of RDS.
2. We are not comfortable defining a directionally concordant trend for secondary endpoints that, used in combination with your primary endpoint, would serve to support Surfaxin registration for this indication.

Please contact the Division to arrange a time to discuss finding another path forward for development of Surfaxin in the treatment of neonatal RDS. Please also submit your March 14, 2001, fax to your IND 40,287.

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

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Christine Yu  
5/24/01 10:46:08 AM  
CSO

## MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 12, 2001  
TIME: 3:00 – 4:30 PM  
LOCATION: Parklawn Conference Room M  
APPLICATION: IND 40,287 Surfaxin (lucinaftant)  
  
BETWEEN: Discovery Laboratories, Inc. (unless noted)

Name: Robert J. Capetola, President/CEO

(b) (4)

Adam Ramage, Senior Regulatory & Quality Associate

(b) (4)

Christopher J. Schaber, Executive Vice President, Drug Development & Regulatory Compliance

Robert Segal, Vice President, Clinical Research & New Drug Evaluation

Huei Tsai, Vice President, Biometrics

AND Division of Pulmonary & Allergy Drug Products (unless noted)

Name: Ray Anthracite, Medical Officer  
Sandy Barnes, Chief, Project Management Staff  
Debra Birenbaum, Medical Officer  
John Jenkins, Director, Office of Drug Evaluation-II  
Lisa Kammerman, Biometrics, Team Leader  
Marianne Mann, Deputy Director  
Timothy McGovern, Pharmacology & Toxicology Reviewer  
Robert Meyer, Division Director  
S. Edward Nevius, Division Director, Biometrics II  
Sue-Jane Wang, Senior Mathematical Statistician  
Christine Yu, Regulatory Project Manager

### Background

November 13, 2000 Discovery submitted protocol KL4-IRDS-04 entitled "A multicenter, randomized, masked placebo-controlled trial comparing the safety and effectiveness of Surfaxin to standard of care in the treatment of Respiratory Distress Syndrome (RDS) in premature infants" (serial 074).

November 27, 2000 Division sends letter to Discovery expressing concerns regarding ethicality of the proposed trial and the applicability of such data to the U.S. population.

December 18, 2000 Discovery and the Division discussed ethicality/approvability of the proposed trial in a teleconference. Discovery provided more information regarding the trial, and the Division requested additional information before a Center level meeting can be scheduled.

January 18, 2001	Revised protocol was submitted in response to Division comments (serial 078).
January 24, 2001	Masked proposed protocol presented as topic of discussion at CDER Scientific Rounds.
February 22, 2001	Sidney Wolfe from Public Citizen sends letter to Secretary Tommy Thompson regarding proposed trial.
February 23, 2001	Discovery requests face-to-face meeting to update the Division on status of neonatal treatment of RDS in Latin America and to clearly present Discovery's rationale and justification for the trial as the Division prepares for the Center level discussion of the proposed trial scheduled March 14, 2001.
March 8, 2001	Discovery faxes "Alternate Surfaxin prophylaxis vs. Survantu rescue superiority trial design" with their meeting briefing package (serial 084).

#### Meeting Agenda

Introductions	(5 min)	Christine Yu
Discovery	(25 min)	C.J. Schaber, R.J. Capetola
DPADP	(15 min)	Dr. Birenbaum
Additional Discussion	(15 min)	
Conclusion		Christine Yu

#### Minutes Format

Appendix A	(b) (4), information folder contents
Appendix B	Discovery's Overheads
Appendix C	Division's Overheads
Appendix D	Division's Handout

#### Minutes

Discovery started their presentation describing general attributes of surfactants. The main ingredient of all surfactant is L- $\alpha$ -dipalmitoylphosphatidylcholine (DPPC), and there is no reason to believe that any particular surfactant will be markedly different from the others. Discovery stated that basic pharmacology does not support a superiority trial. The main question that needs to be addressed is, "How can we bring surfactants to Latin America?" so that all arms in the trial will benefit.

(b) (4) gave an update of the financial and medical limitations that hinder management of RDS in Guayaquil, Ecuador. See Appendix A, page 8. (b) (4) stated that he would like to see the Agency and Discovery work together so that surfactants can be made available to the babies in Latin America.

(b) (4) added that few surfactants approved in the U.S. are used outside of the U.S. Surfactants are very expensive, and although it is desirable to have better outcome in all arms, the reality is, making surfactants available to Latin American infants is the primary goal. There are more deaths due to RDS in one hospital in Latin America than there are in all of the U.S. Additionally, when a trial conducted in Latin America countries have been completed, those countries are back in the same situation as before the trial. There is no long-term benefit or commitment to the countries where the trials were performed.

Discovery stated that the placebo-controlled trial design has now become problematic and presented overheads providing the rationale for the alternate Surfaxin prophylaxis versus Survanta rescue superiority trial design. See Appendix B, Page 12.

The Division stated that the Agency is unhappy that information regarding the placebo-controlled trial design was inappropriately given to Public Citizen. The Division is committed to working with Discovery to find a path forward for the development of Surfaxin. The comments regarding the alternative trial design have not been finalized, but the following are the Division's **preliminary** comments (Appendix C, page 19).

1. The proposed trial is not a simple prophylaxis versus rescue trial.
2. There are continued ethical issues and new trial design and safety concerns.

a. Ethical Issues

- ◆ Standard of care in the U.S. has evolved, and continues to evolve, regarding the optimal timing for surfactant treatment in premature infants who may develop RDS, but there seems to be general agreement that one should use surfactant as soon as possible after developing RDS requiring intubation and mechanical ventilation, rather than waiting for established RDS to worsen.
- ◆ This trial deliberately delays any surfactant treatment in the "sham" arm for at least 6 hours, until patients meet criteria for SEVERE RDS, but allows retreatment with Surfaxin at 4 hours in the prophylactic Surfaxin arm, for less severe RDS.

If ethical concerns were raised with the placebo-controlled design, there will be concerns with this trial design.

b. Trial design Issues

- ◆ Study endpoints can be affected by use of Surfaxin, timing of Surfaxin vs timing of Survanta, use of Survanta, total surfactant dose. Current design may not yield interpretable results.
- ◆ The combined primary endpoint may be driven by "not requiring RDS rescue." The rescue sham arm will have received no surfactant treatment until meeting severe RDS criteria at >6 hours, while the prophylaxis arm may receive up to 2 doses of Surfaxin by 4 hours of age. You have told us that the rate of premature infant mortality is between 40-80% in untreated LA infants. If most of these deaths are due to RDS, it is likely that most surviving sham arm infants will require rescue Survanta for severe RDS.
- ◆ The combined endpoint involves mixing assessments made at two different periods during the trial.

- ◆ A time to event analysis endpoint may be problematic if the ultimate difference between the two arms is not statistically significant, or if the curves appear to be merging. An incidence endpoint should be primary. A time to event analysis may be used as a secondary endpoint, assessing whether there is benefit throughout the period of the endpoint.

### 3. Safety Concern

Premature infants in the Surfaxin prophylaxis arm may receive up to 16 mL/kg of concentrated **surfactant** within 6 hours of birth. It is not clear that a concentrated volume of two different surfactant preparations, over this period of time, will be safely tolerated by this patient population. Studies in rabbits indicated that survival in Surfaxin treated rabbit groups who received 22.8mL/kg (800mg/kg total dose) over 48 hours was less than half the untreated groups.

Additionally, the Division provided the following comments in a handout (Appendix D, page 21).

- A. Additional justification for not conducting Surfaxin versus Exosurf superiority trials in Latin America, using a primary endpoint other than mortality, such as "incidence of air leak," is requested.

All surfactants do not have similar efficacy for all clinically relevant endpoints, even though they share the same basic active component, DPPC.

1. "Therapeutic trials have shown the natural surfactants harvested from animals to be more effective than the currently available synthetic surfactants, and perhaps the more pure natural surfactants to be somewhat more effective than those extracted from lung minces." Kattwinkel, J: Surfactant Evolving Issues. Clinics in Perinatology 25:17-32, 1998.
2. Infasurf demonstrated statistical superiority to Exosurf on clinically relevant endpoints other than overall mortality, which was the basis for U.S. approval. Infasurf demonstrated statistical superiority to Exosurf for treatment of RDS on incidence of air leaks ( $p < 0.001$ ), with an overall mortality at discharge trend advantage seen in the Infasurf arm ( $p = 0.07$ ).
3. Infasurf also demonstrated statistical superiority to Exosurf for prophylaxis of RDS on incidence of RDS ( $p < 0.001$ ), incidence of air leaks ( $p = 0.01$ ), death due to RDS ( $p \leq 0.01$ ), crossover to the other surfactant ( $p \leq 0.001$ ), and lower overall mortality trends seen in the Infasurf arm.
4. A recent European trial comparing the synthetic surfactant, ALEC, with porcine derived Curosurf, demonstrated a significant pre-discharge mortality difference following data safety monitoring committee (DSMC) review midway through the trial (14% vs 31%,  $p = 0.006$ ), leading to discontinuation of the trial and subsequent market withdrawal of ALEC. ALEC contained DPPC and phosphatidyl glycerol in a 7:3 ratio, without other

phospholipid or apoprotein. ALEC had been previously approved in Europe based on showing superiority to placebo.

The Division is concerned that a placebo controlled trial, while establishing efficacy, would not address the possibility that the new surfactant may be inferior to approved therapies, and that its use may lead to greater infant morbidity and mortality in the U.S. This concern is valid for all new surfactants, but particularly those that are synthetically derived, given the aforementioned data.

- B. Please reconfirm your prior statement that no surfactants of any type have been used in any infant treated at a participating Latin America institution, and further clarify whether a placebo controlled trial in Latin America would be discontinued should such therapies become available to non-enrolled patients.

Dr. Packer asked if the data would be considered interpretable if there is no fixed delay. Furthermore, if there is no fixed delay, he inquired whether incidence of RDS would be an acceptable endpoint.

Dr. Birenbaum responded that with such a trial design the timing of the drug still could not be separated from drug effect. Incidence of RDS may be a possible endpoint, but mortality would need to track in the right direction. In one Infasurf/Survanta trial, mortality tracked in the wrong direction. Dr. Birenbaum asked if clinicians would view incidence of RDS as a clinically relevant endpoint.

Dr. Packer stated that RDS is a serious disease. True benefits are observed with timely intervention. The issue is when should the benefit be measured. Since RDS leads to pulmonary interstitial emphysema (PIE) and other adverse events, showing a decrease in RDS should be "clinically relevant."

Dr. Packer stated that there are 2 separate questions that need to be addressed.

- ◆ In what kind of trial design can Surfaxin be ethically, practically be proven to be efficacious?
- ◆ What happens if Surfaxin beats placebo, but is shown to be inferior to a marketed surfactant? A placebo-controlled trial will not address this question.

The Division stated that if Surfaxin can show itself to be more efficacious than Exosurf and also has the added benefits of being cheaper and not animal-derived, then Surfaxin would be a gain for public health. The FD&C act calls for drugs to be proven effective. If Surfaxin is less effective in comparison to currently used surfactants, drug approval will be based on a risk versus the benefit analysis.

The Division also stated that a possible path forward would be a 3-arm trial with Survanta as the reference arm, with preferably a 1:1:1 ratio between the arms. RDS and clinically relevant endpoints would need to be defined. "Western" populations should be included to address data applicability concerns. Pneumothorax and PIE are possible clinically relevant endpoints, although the most clinically relevant endpoint is currently thought to be survival without chronic lung disease.




Discovery responded that PIE is harder to diagnose than RDS. Likewise, using air leaks as an endpoint would be difficult with the gap between groups only 4-5%. Also, powering the study is an issue that cannot be set aside.

**Follow-up**

1. Discovery stated that they will fax to the Division by the following day their proposal for the 3-arm trial.
2. The Division will try to provide comments by the end of the week.
3. The sponsor did not provide a response to the following request from the Division.

Please reconfirm your prior statement that no surfactants of any type have been used in any infant treated at a participating Latin America institution, and further clarify whether a placebo controlled trial in Latin America would be discontinued should such therapies become available to non-enrolled patients.

Submitted by,



Christine Yu, R.Ph.  
Regulatory Project Manager



Food and Drug Administration  
Rockville, MD 20857

IND 40,287

Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

3/9/01  
IR

Attention: Christopher J. Schaber  
Executive Vice President, Drug Development & Regulatory Affairs

Dear Mr. Schaber:

Please refer to your Investigational New Drug Application (IND) submitted August 4, 1992, received August 6, 1992, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant).

We also refer to your November 13, 2000, submission for protocol KL4-IRDS-04 entitled "A multicenter, randomized, masked placebo-controlled trial comparing the safety and effectiveness of Surfaxin to standard of care in the treatment of Respiratory Distress Syndrome (RDS) in premature infants," and to the amendment dated January 18, 2001 (serial # 078), containing a revised protocol.

We have completed the clinical review of your January 18, 2001, submission and have the following comments and requests for additional information.

**Ethical concern about this trial is still under FDA discussion.** We will be discussing this issue with you following our March 14, 2001 internal meeting. The following comments address other concerns about this protocol, should you pursue this trial to support approval in the United States.

1. The Kaplan Meier approach evaluating time to death prior or up to 28 days of age may be problematic if the ultimate 28-day mortality difference between Surfaxin and placebo is not statistically significant, or if the curves appear to be merging. Incidence of all cause mortality evaluated at 28 days or another clinically relevant endpoint should be primary for this trial. Time to death may be used as a secondary endpoint, assessing whether a survival benefit is evident throughout the 28 day period.
2. Clarify how the mortality rate in both the Survanta arm and Surfaxin arm were estimated. Submit premature infant mortality rates in participating Latin American (LA) countries at institutions where surfactants, particularly Survanta, are standard of care.
3. Reliable estimation of the Survanta treatment effect in the LA population, and comparison of that effect to the historical Survanta treatment effect will increase confidence that the results of the LA trial are applicable to the U.S. population. Thus, this arm is considered critical. Further, a comparison of the Survanta treatment effect to the Surfaxin treatment effect should be planned to assess animal derived surfactant versus protein containing synthetic surfactant performance in this LA population. A 1:1:1 randomization is necessary to allow fair

comparison. In addition, it is noted that this will give each infant a 2/3 chance for receiving active drug.

4. A detailed plan for interim analysis should be submitted for formal review.
5. The protocol should specify whether trial data will be unblinded and analyzed prior to completion of the 6 and 12 month follow-up assessments.
6. The probability of dying, as related to RDS, is highest in the first 72 hours following birth. Therefore, infants who die will most likely have very few ventilator days or days on supplemental oxygen. Hence, a true ITT analysis with LOCF (last observation carried forward) may unfairly demonstrate fewer days on the ventilator when, in truth those infants may have died. We recommend that this analysis be performed on both the ITT population and the evaluable population of survivors at 28 days.
7. To limit endpoint confounding for the duration of supplemental oxygen and number of mechanical ventilator days, you should institute standardized parameters for discontinuing supplemental oxygen and parameters for extubation. These should be included in your protocol.
8. Bronchopulmonary dysplasia (BPD) is defined as supplemental oxygen to keep  $\text{SaO}_2 \geq 92\text{-}95\%$ . The protocol should clearly define an upper limit for oxygen saturation on supplemental oxygen (e.g. supplemental oxygen to keep  $\text{SaO}_2 \geq 92$  and  $\leq 95\%$ ).
9. All air leaks, regardless of whether they are resolved with a chest tube, should be tracked and evaluated. It would also be informative to track and evaluate all air leaks that require a clinical intervention (e.g. chest tube placement, needle aspiration, change to high frequency ventilation).
10. Criteria for determining the presence of RDS on chest x-ray should be prospectively defined in the protocol. Further, the protocol should state that evaluation of all x-rays will be made by a qualified clinician masked to treatment assignment.
11. The protocol should specify the maximum time Surfaxin may remain unrefrigerated and warmed, prior to administration to the infant.
12. Preparation for Surfaxin administration should include a step for flushing Surfaxin through the end-hole catheter prior to administering the first 2.9 mg/kg dose. Since the protocol specifies that the catheter is not flushed at the end of the dosing procedure, less than the specified dose will be administered if this step is omitted.
13. Your trial should assess immunogenicity of Surfaxin in human infants. The 21 peptide chain that constitutes KL-4 peptide has theoretical immunogenic potential.
14. The protocol should state whether or not **synthetic** surfactants may be available to infants in those regions where you claim “no routine use” of **animal**-derived surfactants (page 83 of the

submission dated January 18, 2001). Please clarify whether or not “**no routine use**” means that there is **no** use.

15. Page 95 of the January 18, 2001, submission refers to the “beneficial effects of treatment” when describing a requirement to adjust FiO<sub>2</sub> and ventilator pressures following dosing. The term “beneficial” should be omitted from the protocol. The protocol should alert investigators to the possibility that treatment procedures in all three trial arms may result in the need for clinicians to modify therapy, in response to clinical changes in their patients.
16. An investigator’s brochure, sample case report forms (CRFs), and sample informed consent forms should be submitted to the Agency in English when they become available. Also submit the central US IRB approval letter.

If you have any questions, call Ms. Christine Yu, Regulatory Project Manager, at 301-827-1051.

Sincerely,

*{See appended electronic signature page}*

Robert J. Meyer, M.D.

Director

Division of Pulmonary and Allergy Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

/s/

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Robert Meyer

3/9/01 02:55:08 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 11, 2001

**To:** Christopher Schaber  
Executive VP, Drug Development &  
Regulatory Compliance

**Company:** Discovery Laboratories

**Fax number:** 215-340-3940

**Phone number:** 215-340-4699 x-130

**From:** Christine Yu, R.Ph.  
Project Manager

Division of Pulmonary and Allergy Drug  
Products

**Fax number:** 301-827-1271

**Phone number:** 301-827-1051

**Subject:** Minutes of teleconference on December 18, 2000

**Total no. of pages including cover:** 5

**Comments:**

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**Document to be mailed:**

☐ YES

☒ NO

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Memorandum of Telephone Facsimile Correspondence

Date: October 12, 2000

To: Christopher Schaber  
Executive Vice President, Drug Development & Regulatory Compliance

Fax: 215-340-3940

From: Christine Yu  
Project Manager

Subject: IND 40,287 Surfaxin RDS Latin America trial  
Revised minutes of teleconference August 9, 2000

Reference is made to the teleconference held between representatives of your company and this Division on August 9, 2000. Attached is a copy of our final minutes for that teleconference. These minutes will serve as the official record of the teleconference.

If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

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Thank you.

INDUSTRY TELECONFERENCE MINUTES

IND: 40,287  
Drug: Surfaxin (lucinactant) Intratracheal Suspension  
Date: August 9, 2000  
Sponsor: Discovery Laboratories, Inc.

FDA Participants: Debra Birenbaum, Medical Reviewer  
Badrul Chowdhury, Acting Team Leader  
Martin Himmel, Deputy Office Director, OPDRA  
Sue-Jane Wang, Senior Mathematical Statistician  
Steve Wilson, Team Leader, Biostatistician  
Christine Yu, Project Manager

Sponsor Participants: Christopher Schaber, Executive Vice President,  
Drug Development & Regulatory Compliance  
Robert Segal, Vice President, Clinical Research  
Huei Tsai, Vice President, Biometrics

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Background: Discovery and the Agency have had numerous discussions regarding proposed protocols for the Surfaxin RDS trials. Discovery stated that they are currently conducting feasibility studies for a placebo-controlled RDS trial in Latin America in countries where surfactant use is not standard of care. The Division initiated this telecon to obtain more information about Discovery's plans for such a trial. Discovery's brief overview of their plans is followed by questions (in *Italics*) by the Division #1-5, Discovery #6, and subsequent discussion (regular font).

The minutes were faxed to the sponsor August 30, 2000. Christopher Schaber from Discovery left a voice mail message clarifying several points in response to the Division's minutes. These revised minutes reflect Discovery's clarifications, noted in bold font.

\*\*\*\*\*

Christopher Schaber introduced Dr. Robert Segal, the new medical monitor. Dr. Segal comes from Merck with cardiovascular expertise. He has been with Discovery for about four weeks.

Discovery stated that they are conducting preliminary investigations to see if the trial would be feasible in Latin America. The sponsor envisions this trial as Surfaxin versus standard of care in institutions where surfactants are not used to treat RDS in premature infants.

Discovery is considering this trial in Mexico, Panama, Ecuador, Peru, and **Bolivia**.

**Argentina will not be one of the countries considered for the trial; they have a higher standard of care more in line with U.S. standards.** Latin American clinicians surveyed



by Discovery have given favorable responses to the proposed study. Discovery is in the process of retrieving institutional data on mortality rate and premature birth rate. One pivotal trial, powered to 90% or greater, is being planned. The endpoints being considered include mortality and bronchopulmonary dysplasia (BPD) at 36 weeks post conceptual age.

1. *Where is Discovery planning to submit applications for Surfaxin approval based on this proposed trial?*

Discovery plans to follow GCP, FDA and ICH guidelines and will submit this protocol to the IND. The company ultimately will seek approval in (b)(4), Europe and the U.S.

2. *Institutional Review Boards (IRBs) of which countries would be involved in the proposed trial?*

Discovery responded that they will be working with the IRBs of the Latin American countries. Some countries have national IRBs that review the protocols submitted into their country. U.S. IRBs will not be involved. A scientific advisory board will be involved in designing this study, and a Data Safety Monitoring Board (DSMB) is planned for continual evaluation of safety. **In addition to the DSMB and scientific advisory board, a steering committee made up of key individuals in Latin America (possibly including committee members from Argentina) is also being planned.**

The sponsor stated that surfactants have been approved and used in some of the countries mentioned, but the institutions being considered do not use those surfactants because of financial constraints.

The Division reminded Discovery that they must adhere to the Declaration of Helsinki.

3. *How does the standard of care differ from the NICUs in the U.S.?*

Discovery estimated that the premature infant mortality is approximately 30-40% in the countries mentioned. Although medical equipment is not the best available and there are limits in the number of ventilators and resources available at the institutions being considered for trial participation, Discovery stated that the standard of care is generally comparable to care in the U.S. They plan to use institutions where the level of care would be comparable.

The Division stated standard of care comparability would need to be supported. Significant differences between levels of care may raise questions about the applying the results of the trial in South America to patients in the U.S.

Discovery plans to send training teams to Latin America that would include neonatologists trained in the U.S. Discovery is also planning to assemble a team of local and key physicians of that region so that the standard of care can be comparable.

4. *What surfactants are approved in the Latin America countries?*

Survanta, Curosurf and Exosurf are approved in Argentina. **Surfactants have also been approved in other countries. In countries being considered for the trial, surfactants are available in key institutions or rationed by the government.**

5. *Is Discovery still pursuing non-inferiority RDS Surfaxin trials in the U.K. (United Kingdom)?*

Discovery is still pursuing European trials. **They have filed the package to the EMEA for review and are waiting for feedback from the CPMP.**

6. *Is a single, high-powered trial sufficient to meet regulatory approval?*

The Division replied that it is premature to answer this question. There are multiple informational and ethical questions that the Division will need to consider and discuss internally. However, the Division did state that other surfactant sponsors had conducted multiple trials, and it would be ideal to have two trials. ALEC (pumactant), which was approved in England based on a single, placebo-controlled trial, now has safety concerns subsequent to a post-marketing trial versus Curosurf. The trial was halted due to mortality rate in ALEC that was twice the natural surfactant. The clinical use of ALEC in the UK has been recently suspended.

Discovery will continue to collect more data and submit their protocol when it is ready.

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Christine Yu, R.Ph.  
Project Manager

*(This section will not be communicated to the sponsor.)*

Post-telecon internal discussion of concerns:

- 1.
- 2.
- 3.
- 4.

(b) (5)

Dr. Himmel recommended an Office level internal discussion regarding these concerns before Discovery submits a protocol. The meeting would include the DPADP team, Drs. Martin Himmel, John Jenkins, Hsien W. Ju (from DSI), and Dianne Murphy.

cc: IND 40,287  
HFD-570/Division files  
HFD-570/Birenbaum  
HFD-570/Chowdhury  
HFD-400/Himmel  
HFD-570/Meyer  
HFD-715/Wang  
HFD-715/Wilson  
HFD-570/Yu

Drafted: cy/August 16, 2000

Concurrence: Birenbaum/August 25, 2000  
Himmel/August 29, 2000  
Chowdhury/August 29, 2000  
Wang/August 29, 2000  
Wilson/August 29, 2000

Revision: cy/October 4, 2000

Concurrence: Birenbaum/October 6, 2000  
Himmel/October 10, 2000  
Chowdhury/October 10, 2000  
Wang/October 10, 2000  
Wilson/October 10, 2000

Final: cy/October 12, 2000

Filename: I40287RDStele080900

## INDUSTRY TELECONFERENCE MINUTES

**IND:** 40,287  
**SPONSOR:** Discovery Laboratories  
**DRUG:** Surfaxin (lucinactant)  
**DATE:** April 14, 2000

**FDA PARTICIPANTS:** Debra Birenbaum, Medical Reviewer  
Martin Himmel, Deputy Division Director  
Robert Meyer, Division Director  
S. Edward Nevius, Director, Division of Biometrics II  
Sue-Jane Wang, Biometrics Reviewer  
Christine Yu, Project Manager

**SPONSOR PARTICIPANTS:** Robert Capetola, President and CEO  
Christopher Schaber, Executive Vice President, Drug  
Development and Regulatory Compliance  
Huei Tsai, Vice President, Biometrics  
Thomas Wiswell, Executive Vice President, Clinical  
Research & Development

### Background:

March 28, 2000, Discovery Laboratories faxed to the Division "Alternative Proposal: Non-inferiority study of Surfaxin vs Survanta using a prophylaxis strategy." The sponsor also submitted a supplement to the protocol proposal on April 7, 2000. The Agency held an internal meeting to discuss the non-inferiority trial proposal on April 13, 2000. The Division comments regarding the proposal were faxed to Discovery on April 18, 2000 (see attached). The purpose of the teleconference was to provide Division concerns regarding the non-inferiority proposal.

The Division opened the discussion with an inquiry about any additional information or data to help estimate temporal change in the effect size. Discovery stated that no new reliable data are available.

The Division provided six comments to the protocol.

In response to the fifth comment, the sponsor stated reasons Surfaxin will have potential benefits over the marketed surfactants:

1. Surfaxin mimics human protein SP-B.
2. Surfaxin does not pose risk of antigenicity. (based on animal studies and knowledge that neonates are relatively poor immunologic responders).
3. Surfaxin has advantages because it is not animal derived.

- a) Surfaxin is not oxidized, therefore, it is less subject to inactivation if nitric oxide is used with a surfactant.
- b) Manufacturing can be accomplished with tighter specifications and in unlimited quantities.
- c) Fewer doses may be required

The Division stated that the benefits mentioned may not translate into clinically relevant benefits to the child. To allow for any increase in mortality, there must be potential gain in clinically relevant endpoints.

Discovery stated that it appears an equivalency trial is not possible, only a superiority trial, although the proposed trial of 2000 subjects would be the largest neonatal surfactant trial known.

The Division stated that the comments for the non-inferiority trial proposal would have to be addressed. Since a non-inferiority trial does not appear to be feasible, the OSIRIS model was again offered as an option.

The Division proposed that written comments be faxed to the sponsor and a follow up discussion take place.

The Division summarized by stating that they understand Discovery faces a difficult situation where a placebo trial is no longer ethical. However, clinical benefit, not just pharmaceutical benefits of the drug, must clearly be demonstrated. Finally, the choice of an appropriate percentage of effect size to be preserved in a non-inferiority trial poses a difficult regulatory issue. The Division again recommended a Surfaxin prophylaxis vs Surfaxin rescue superiority trial, which may show the benefits of dosing strategy, support efficacy and provide for a cleaner study. The Division will continue to work with the sponsor for further drug development.

#### **Action**

1. Division to fax comments on Tuesday, April 18, 2000.
2. Discovery to contact the Division for further discussion on the comments or recommendations.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 40,287

11/27/00  
Advice

Discovery Laboratories, Inc.  
350 South Main Street, Suite 307  
Doylestown, PA 18901

Attention: Christopher J. Schaber  
Executive Vice President, Drug Development & Regulatory Compliance

Dear Mr. Schaber:

Please refer to your Investigational New Drug Application (IND) submitted August 4, 1992, received August 6, 1992, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinactant).

Reference is made to our teleconference with you on August 9, 2000, regarding IND 40,287. You informed the Division that you are in the process of evaluating whether it was logistically and ethically possible to perform a Surfaxin vs. placebo trial for the treatment of premature infants with Respiratory Distress syndrome in certain Latin American countries. We informed you at that time that there were multiple informational and ethical questions that the Division will need to consider about the conduct of such a proposed trial.

A preliminary meeting was held on November 7, 2000, with members of our Division, as well as representatives from the Office of Drug Evaluation II, the Division of Scientific Investigations, and the Pediatric Subcommittee to discuss your planned investigation in Latin America. Serious ethical concerns, related to the use of a placebo-control trial in a Latin American population, were expressed at this meeting (as well as concerns about the applicability of such data to the U.S. population).

Several documents were considered during the November 7, 2000, meeting, including the newly revised Declaration of Helsinki, the September 29, 2000, draft report from the National Bioethics Advisory Commission entitled, "Ethical and Policy Issues in International Research," and the ICH E10 document. The latter document raises specific concerns as to whether your proposed trial will conform to regulatory policy and be acceptable for supporting U.S. registration of Surfaxin. Specifically, this document states,

"When a new agent is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new agent to placebo. Use of a placebo control may raise problems of ethics, acceptability and feasibility, however, when an effective treatment is available for the condition under study in a proposed trial. In cases where an effective treatment is known to prevent serious harm, such as death

or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control. There are occasional exceptions, however, such as cases in which standard therapy has toxicity so severe that many patients will refuse therapy.” (ICH E10 2.1, 2.1.3)

The concerns over the applicability of Latin American data to the U.S. population include the following:

1. whether the high rate of neonatal mortality seen in premature Latin American infants is reflective only of surfactant-related standard of care differences;
2. whether it is possible to correct other aspects of “substandard care” if Latin American doctors receive training by U.S. neonatologists;
3. whether uncorrected maternal factors and prenatal management differences in care between Latin America and the U.S. may impact neonatal mortality;
4. whether bias in an imperfectly masked trial may have a negative impact in the level of care actually delivered to “Standard of Care (SOC)” infants, and in turn, impact overall mortality differences (e.g., would investigators be less likely to escalate care in SOC infants?);
5. whether Latin American neonatologists may assume that exogenous surfactant has benefit over placebo, also resulting in bias.

Additional discussion, both with representatives of Discovery Laboratories as well as within the Agency, will likely be necessary to fully resolve these concerns. If the proposed trial is intended to support U.S. approval, we strongly suggest a teleconference or meeting prior to you proceeding further with the Latin American trial.

If you have any questions, call Ms. Christine Yu, Regulatory Project Manager, at 301-827-1051.

Sincerely,

Robert J. Meyer, M.D.  
Director  
Division of Pulmonary and Allergy Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

/s/

-----  
Robert Meyer

11/27/00 11:22:32 AM



**FOOD & DRUG ADMINISTRATION  
OFFICE OF EVALUATION II**

**Memorandum of Telephone Facsimile Correspondence**

Date: April 18, 2000

To: Christopher Schaber  
Executive Vice President, Drug Development & Regulatory Compliance

Phone: 215-340-4699  
Fax: 215-340-3940

From: Christine Yu, R.Ph.  
Project Manager

Through: Gretchen Trout *EST 4-18-00*  
Acting Chief, Project Management Staff

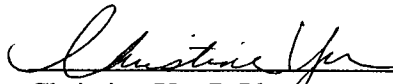
Subject: Agency comments for Surfaxin Non-inferiority RDS trial

Pages: 3 (including cover sheet)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.** If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPADP, Rockville, MD 20857.

Thank you.

  
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Christine Yu, R.Ph.  
Project Manager  
Division of Pulmonary and Allergy Drug Products

**AGENCY CONCERNS ABOUT THE CURRENT PROPOSAL FOR  
NON-INFERIORITY TRIAL OF PROPHYLAXIS SURFAXIN VS  
RESCUE SURVANTA IN THE TREATMENT OF RDS**

1. Changes in the effect size (i.e. the actual benefit of surfactant use) over the past decade are extremely difficult to determine with certainty.
  - ◆ Vital Statistics data may not be reliable when examining cause specific mortality. There are no universal definitions for RDS-related mortality in these statistics, and these data depend on clinical reporting.
  - ◆ The rate of RDS-related death from the data over the past 10 years is not linear. Over the period between 1990 and 1998, it is not possible to reliably identify the year from which one should begin to calculate the non-surfactant related changes (e.g., antenatal-steroids, other clinical management changes) to project the putative mortality rates in the Survanta treatment arm, and thus a reasonable effect size for Survanta vs. placebo in the year 2000. As an example, using the percent change seen between 1993 and 1998 (39%) will yield very different estimates than using the percent change seen between 1995 and 1998 (10%) for a Survanta-treated arm. In addition, no data are available for 1999 and 2000.
  - ◆ The estimation of the change in mortality due to non-surfactant related changes in neonatal care for the "placebo arm" is arbitrary.

For all these reasons, there is significant uncertainty in choosing a presumed effect size for Survanta in the year 2000. This uncertainty and the resultant arbitrary nature of choosing a putative year 2000 effect size undermines all other calculated assumptions in developing a non-inferiority approach.

2. Preservation of 50% of the effect size for a mortality endpoint may not be adequate for this trial. The 50% value was mentioned at a previous meeting between the Agency and Discovery Laboratories as an example of what had been used for certain cardiovascular drugs that had been reviewed in the past. At that meeting, Dr Temple himself stated that he did not know if such a number was appropriate given the differences in the populations. He deferred to subject experts on the matter of an appropriate amount of the effect size one wanted to assure was preserved. Clearly, increasing the percentage that one wants to assure is preserved will significantly impact the sample size.

3. All statistical estimates are based on Study 2 in the Survanta RDS prevention trials. Although the Agency asks that the company use the most conservative approach, overall mortality did not track with RDS related mortality in Study 2. Thus the actual estimate of the Survanta effect size is based on limited data.
4. Death due to RDS criteria were not prospectively defined in the Survanta trials. Therefore it is impossible to establish identical criteria for this study.
5. The potential benefit of Surfaxin over the existing approved surfactants on clinically relevant endpoints is not clear to the Agency. Therefore, one would want to be as conservative as possible in the approach to defining an "acceptable" increase in mortality in conducting a non-inferiority trial.
6. The Agency suggests that you reconsider your position against conducting a superiority trial. Another option for trial design is a "prophylaxis **Surfaxin** vs rescue **Surfaxin**" approach, in a large trial similar to the OSIRIS model. Demonstrating that prophylactic use of Surfaxin is statistically superior to rescue therapy with Surfaxin on clinically relevant endpoints would support the efficacy of prophylactic use of Surfaxin. This concept is similar to a dose response trial in which high doses of a drug are found to be superior to lower doses of the same drug, and thus efficacy is demonstrated for the higher doses.

IND 40,287  
Page 4

cc: IND 40,287  
HFD-Division files 40287  
HFD-570/Birenbaum  
HFD-570/Himmel  
HFD-570/Meyer  
HFD-570/Wang  
HFD-570/Nevius  
HFD-570/Wilson  
HFD-570/Jafari  
HFD-570/Yu

Initialed by: Birenbaum/April 17, 2000 *24*  
Himmel/April 17, 2000  
Meyer/April 17, 2000 *msh*  
Wang/April 17, 2000 *4/18/00*

Filename: I40287noninfcomm041800

05 89A

05 89A

IND 40,287

**Memorandum of Telephone Facsimile Correspondence**

Date: January 13, 2000

To: Christopher J. Schaber  
Executive Vice President, Drug Development and Regulatory Compliance

From: Ladan Jafari  
Project Manager

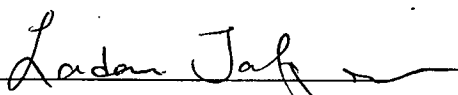
Through: Parinda Jani  
Acting Chief, Project Management Staff

Subject: Proposed equivalency prevention study comparing Surfaxin with Survanta

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

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Thank you.

  
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Ladan Jafari  
Project Manager  
Division of Pulmonary and Allergy Drug Products

Discovery has requested Agency input about a new proposed endpoint, incidence of survival or no death due to Respiratory Distress Syndrome (RDS), and a proposed equivalency margins. The following comments reflect the Agency's concerns and suggestions. We look forward to meeting with you on Friday so that we may further discuss these issues.

1. The effect size seen in studies performed a decade ago may not remain valid for a trial done today. Issues that may impact the endpoint include:
  - a. Increased use of maternal steroids in the past decade. Surfactant plus a completed course of prenatal steroids has been shown to improve outcome beyond the use of either therapy alone. It is not possible to reliably know how that effect size has changed relative to placebo.
  - b. Improved clinical management of pre-term infants in the past decade. These changes may also impact the effect size seen in the early surfactant trials. It is not possible to perform an equivalency trial unless the effect size is reliably known.
  - c. The proposed equivalency margin is not justified because it is too wide to offset those concerns. A narrower margin would result in very large trial that may be impractical to complete.
2. Criteria to establish death due to RDS were not prospectively stated in the original Survanta trial protocols. Cause of death was assigned by a mortality review board, in which 2/3 panel members had to agree. It is unclear what criteria the review board prospectively established to assign cause of death, thus it is not clear that the same set of criteria can be applied in this trial
3. Overall mortality did not track with death due to RDS in Study 2. In fact, overall mortality was greater in the Survanta treated infants.

The Division suggests the following alternatives, in lieu of any equivalency trial:

1. prophylaxis vs. rescue superiority trials
2. Surfaxin vs Exosurf superiority trials in Europe
3. Surfaxin vs Infasurf superiority trials in the US
4. Surfaxin vs Curosurf superiority trials in the US and/or Europe

IND 40,287

Page 3

cc:

IND 40,286

Div. Files

HFD-570/Birenbaum

HFD-570/Himmel

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HFD-570/Yu

Initialed by: Jani/1-12-00

Filename: discoverycomments