

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021746Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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.)

Section A: 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 [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<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)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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 †
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 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.)

Section A: 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 [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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 †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<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)

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

/s/

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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/s/

Christine Yu

1/31/05 05:30:31 PM



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

FACSIMILE TRANSMITTAL SHEET

Date: March 2, 2012

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

Subject: NDA 21-746 Surfaxin Draft label comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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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)
IMMEDIATELY FOLLOWING THIS PAGE

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/s/

ANGELA H RAMSEY
03/02/2012



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

FACSIMILE TRANSMITTAL SHEET

Date: February 28, 2012

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

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

Total no. of pages including cover:

Comments:

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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/

ANGELA H RAMSEY
02/28/2012



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

FACSIMILE TRANSMITTAL SHEET

Date: February 17, 2012

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

Subject: NDA 21-746 Draft label comments

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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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

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

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/s/

ANGELA H RAMSEY
02/17/2012



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

FACSIMILE TRANSMITTAL SHEET

Date: February 13, 2012

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

Subject: NDA 21-746 (Surfaxin) IR fax

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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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.

Drafted by: AR/February 13, 2012
Initialed by: SB/February 13, 2012; TD/February 13, 2012;

Finalized: AR/February 13, 2012

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/s/

ANGELA H RAMSEY
02/13/2012



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

FACSIMILE TRANSMITTAL SHEET

Date: February 9, 2012

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

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

Total no. of pages including cover:

Comments:

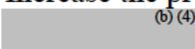
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NDA 21-746

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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/s/

ANGELA H RAMSEY
02/09/2012



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

FACSIMILE TRANSMITTAL SHEET

Date: January 31, 2012

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

Subject: NDA 21-746 Draft label

Total no. of pages including cover:

Comments:

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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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/s/

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/

CAROL A HOLQUIST
01/24/2012

Patwardhan, Swati

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 [REDACTED] (b) (4) as the sole performer of the Biological Activity Testing, yet the Inspection Report audit from this site provides the [REDACTED] (b) (4) for the [REDACTED] (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/

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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/s/

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}

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/

PHILANTHA M BOWEN
12/29/2011



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2011

To: Russell Clayton Sr, D.O. Acting Head, Regulatory Affairs	From: Angela Ramsey Regulatory Project Manager
Company: Discovery Laboratories	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 215-488-9301	Fax number: 301-796-9728
Phone number: 215-488-9470	Phone number: 301-796-2284
Subject: 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 or by calling 301-796-2284

Document to be mailed: YES xNO

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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 (b) (4).
 - d. Change the description for the X and Y axes to *log KL₄ concentration* and *efficacy (%C_{RS})*, 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) 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/

ANGELA H RAMSEY
12/23/2011

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Angela Ramsey Senior Regulatory Project Manager OND/DPARP 301-796-2284
------------------------------	---

REQUEST DATE November 14, 2011	IND NO.	NDA/BLA NO 21-746.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
-----------------------------------	---------	-----------------------	---

NAME OF DRUG Surfaxin (lucinactant) Intratracheal Suspension	PRIORITY CONSIDERATION Priority	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
---	---------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (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)	TYPE OF APPLICATION/SUBMISSION <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	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
--	---	---

EDR link to submission:
 \\cdsesub4\NONECTD\NDA021746\4925023\Labeling

Please Note: 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.

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/

ANGELA H RAMSEY
11/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO (*Division/Office*): **New Drug Microbiology Staff**

***E-mail to:* CDER OPS IO MICRO**
***Paper mail to:* WO Bldg 51, Room 4193**

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

Surfaxin (lucinactant)

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

- | | |
|---|---|
| <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED | <input type="checkbox"/> CBE-0 SUPPLEMENT |
| <input type="checkbox"/> NDA FILING REVIEW NEEDED BY: _____ | <input type="checkbox"/> CBE-30 SUPPLEMENT |
| <input type="checkbox"/> BUNDLED | <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY |
| <input type="checkbox"/> DOCUMENT IN EDR | |

Jackets will be delivered to assigned reviewer

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):

DARRTS EDR E-MAIL MAIL HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR E-MAIL MAIL HAND

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/s/

ANGELA H RAMSEY
11/02/2011

REQUEST FOR CONSULTATION

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

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 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 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 (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <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 (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: 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)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

ANGELA H RAMSEY
10/21/2011

Patwardhan, Swati

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/

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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/s/

ANGELA H RAMSEY
09/28/2011

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.pdf (163 KB)



VALPROT72.pdf (3 MB)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> X MAIL <input type="checkbox"/> 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 [REDACTED]^{(b) (4)}¹. The pervasiveness and egregious nature of the violative practices by [REDACTED]^{(b) (4)} has led FDA to have significant concerns that the bioanalytical data generated at [REDACTED]^{(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 [REDACTED]^{(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 [REDACTED]^{(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.

¹ These violations include studies conducted by [REDACTED]^{(b) (4)} national specific to the [REDACTED]^{(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/

SANDRA L BARNES
09/13/2011

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.

SIGNER'S NAME
TITLE

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/s/

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



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

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) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

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.

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)
[REDACTED] 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/

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 (lucinaquant) 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)



19 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS)
IMMEDIATELY FOLLOWING THIS PAGE

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/s/

Lori Cantin
4/14/2008 02:53:02 PM
CSO

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising and Communications**

FROM (Name, Office/Division, and Phone Number of Requestor):
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

DATE OF DOCUMENT
October 31, 2007

NAME OF DRUG
Surfaxin

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
1

DESIRED COMPLETION DATE
April 15, 2008

NAME OF FIRM: **Discovery**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 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 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 (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <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 (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: 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
Lori Garcia

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

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 (lucinaquant)

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG
1

DESIRED COMPLETION DATE
April 15, 2008

NAME OF FIRM: Discovery

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

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

IV. DRUG EXPERIENCE

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

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

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please perform DMETS review of NDA 21-746 (resubmission) for Surfaxin (lucinaquant) 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.

PDUFA DATE: May 1, 2008

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: 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)

DFS ONLY MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

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/

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/

Ali Al-Hakim

1/11/2008 01:26:10 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Pharmaceutical Science and
New Drug Microbiology Staff**

FROM (Name, Office/Division, and Phone Number of Requestor): **Angela
Robinson, OND/DPAP
301-796-2284**

DATE
11/05/08

IND NO.

NDA NO.
21-746

TYPE OF DOCUMENT
Class 2 Resubmission

DATE OF DOCUMENT
10/17/08

NAME OF DRUG
Surfaxin (lucinactant)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
2/27/09

NAME OF FIRM: **Discovery Labs**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 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 (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <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 (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: 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.

PDUFA Goal Date: April 17, 2009

SIGNATURE OF REQUESTOR
Angela Robinson

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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

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/s/

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

REQUEST FOR CONSULTATION

TO (Office/Division):
OPS/NDMS, HFD-805
WO Bldg 21

FROM (Name, Office/Division, and Phone Number of Requestor):
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**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 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 (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <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 (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: 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.

PDUFA goal date: May 1, 2008.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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/

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/

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



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/

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

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/s/

Eugenia Nashed
11/22/2005 06:06:58 PM



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

FACSIMILE TRANSMITTAL SHEET

DATE: November 22, 2005

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

Comments:

Document to be mailed: YES NO

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We refer to your NDA 21-746 for Surfaxin (lucinaftant) 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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/s/

Christine Yu
11/22/2005 04:00:22 PM
CSO

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/s/

Christine Yu
11/2/2005 06:29:41 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34		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 (lucinaquant) Intratracheal Suspension		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE February 13, 2006
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 checked="" type="checkbox"/> OTHER: Trade name review				
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 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.				
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/

Christine Yu
11/2/2005 05:48:32 PM

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/s/

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



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/

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 16, 2005

To: Katherine Tsokas, J.D. Director, Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager
Sponsor: Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 215-488-9512	Fax number: 301-827-1271
Phone number: 215-488-9350	Phone number: 301-827-1051
Subject: NDA 21-746 Surfaxin (lucinaftant) Submission dated July 29, 2005	

Total no. of pages including cover: 3

Comments:

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.

We acknowledge receipt of your submission to NDA 21-746 for Surfaxin (lucinaquant) 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/

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



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 11, 2005

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

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

Total no. of pages including cover: 2

Comments:

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/

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/

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 6, 2005

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

Christine Yu
1/6/05 03:52:11 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 28, 2004

To: Katherine Tsokas Director, Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager
Company: Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 215-488-9512	Fax number: 301-827-1271
Phone number: 215-488-9350	Phone number: 301-827-1051
Subject: IND 40,287 Surfaxin in MAS Clinical Information Request	
Total no. of pages including cover: 2	

Comments:

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/

Christine Yu
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CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 14, 2004

To: Katherine Tsokas Director, Regulatory Affairs	From: Christine Yu, R.Ph. Regulatory Project Manager
Company: Discovery Laboratories, Inc.	Division of Pulmonary & Allergy Drug Products
Fax number: 215-488-9301	Fax number: 301-827-1271
Phone number: 215-488-9350	Phone number: 301-827-1051
Subject: NDA 21-746 Surfaxin Request for clarification	

Total no. of pages including cover: 2

Comments: * *Please submit a response no later than Friday, December 17, 2004* *

Document to be mailed: YES NO

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We refer to your NDA 21-746 for Surfaxin (lucinaftant) 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/

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.

[REDACTED] (b) (4)

[REDACTED]

The teleconference concluded at this time.

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/s/

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 22, 2004

To: Katherine Tsokas Director, Regulatory Affairs	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 x229	Phone number: 301-827-1051
Subject: NDA 21-746 Surfaxin Request for information	

Total no. of pages including cover: 3

Comments:

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.

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/s/

Christine Yu
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/s/

Christine Yu
11/19/04 11:27:08 AM



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FACSIMILE TRANSMITTAL SHEET

DATE: November 2, 2004

To: Katherine Tsokas Director, Regulatory Affairs	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 x229	Phone number: 301-827-1051

Subject: NDA 21-746 Surfaxin
Request for information

Total no. of pages including cover: 2

Comments:

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/

Christine Yu
11/2/04 04:10:59 PM
CSO

REQUEST FOR CONSULTATION

TO (Division/Office):

Division of Drug Marketing, Advertising and Communication, HFD-42, PKLN Room 17b-17

FROM:

**Christine Yu, R.Ph.
Regulatory Project Manager, HFD-570**

DATE
20 July 2004

IND NO.

NDA NO.
21-746

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
13 April 2004

NAME OF DRUG
**Surfaxin (lucinafant)
Intratracheal Suspension**

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
1

DESIRED COMPLETION DATE
20 October 2004

NAME OF FIRM: **Discovery Laboratories, Inc.**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV 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 (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

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.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Christine Yu

7/21/04 05:11:08 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34		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 (lucinaquant) Intratracheal Suspension		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE 16 October 2004
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): Trade name review				
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 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		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Christine Yu

7/16/04 01:29:29 PM

REQUEST FOR CONSULTATION

TO (Division/Office):

Peter Cooney, Ph. D.
Microbiology, HFD-805

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 (lucinactant)
Intratracheal Suspension**

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
1

DESIRED COMPLETION DATE
16 October 2004

NAME OF FIRM: **Discovery Laboratories, Inc.**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV 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 (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

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.

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METHOD OF DELIVERY (Check one)

MAIL

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SIGNATURE OF RECEIVER

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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

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2004

To: Katherine Tsokas Director, Regulatory Affairs	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 x-229	Phone number: 301-827-1051
Subject: NDA 21-746 Surfaxin Clinical Information Request	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: YES NO

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, 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.

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/

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 (lucinaftant) 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/

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/

Badrul Chowdhury
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