

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021746Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Transfer responsibility from Discovery to (b) (4) (b) (4) for quality assurance (QA) and data analysis of the analytical method for testing biological activity of the drug product (Method DP-032). Your final study report to support transfer of responsibility should be submitted as a Prior Approval Supplement (PAS) . Your PAS should include a statement that that the analytical facility at (b) (4) is ready for inspection and is qualified to assume full responsibility for all functions related to Method DP-032, consistent with current good manufacturing practices (CGMPs) including data QA and analysis. The transfer of responsibilities from Discovery to (b) (4) will occur upon review and approval of the PAS by the Agency.

PMR/PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 01/30/2014
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The method for biological activity testing of the drug product is pivotal for the regulatory controls and was used for bridging the efficacy of the current drug product to the drug product used in the clinical; trials. The testing is currently carried out by two different sites. The experimental part of the method (tests on premature rabbits) is performed at the (b) (4) site (b) (4), whereas the raw data calculations, data analysis and data reporting is carried out by the Applicant, Discovery Labs, at Warrington, PA. Although each site received an acceptable status for approval from the ORA, the appropriate procedures for data collection and documentation have to be developed and reevaluated by the Office of Compliance. Since no changes are planned to the method itself the proposed changes for the transfer of responsibilities for the quality assurance and data analysis are appropriate for evaluation as a post-approval change and should not impact drug product safety.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The proposed change will be submitted as a prior approval supplement (PAS) with summary of the completed personnel training, installation of additional equipment, implementation of appropriate standard operating procedure for data analysis, documentation practices, deviation and investigation, and corrective and preventive action reports. The PAS application will be evaluated by the CMC review team and by the Office of Compliance, with input, as needed, from the Pharmacology & Toxicology and Clinical review teams.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Transfer responsibility from Discovery to (b) (4) for quality assurance and data analysis of the analytical method for testing biological activity of the drug product (Method DP-032).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

SALLY M SEYMOUR
03/06/2012

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name: Discovery Laboratories, Inc.
City, State: Warrington, Pennsylvania
Inspection Dates: 2/21-24/2012

Inspection Highlights:

- The sponsor needs to improve its documentation practices of notebooks for unexpected events to justify invalidating data and repeating runs.
- With few exceptions, the data submitted to the Agency to support the validation of Method DP-032 were found to be accurate.
- Although Report METHVAL-52 contained a signed compliance statement stating that it was conducted in compliance with Good Laboratory Practice regulations, Method DP-032 was not conducted in compliance with 21 CFR Part 58.

Studies Audited During This Inspection

Application: NDA 21-746
Review Division: DPARP
Testing Facility: (b) (4)
Sponsor: Discovery Laboratories Inc., Warrington, PA 18976
Test Article: KL₄ (Lucinactant)
Study Number: Method DP-032 (VALPROT-72, VALPROT-85, VALPROT-86)
Study Title: In Vivo Biological Activity Test for KL₄ Surfactant Drug Product

Background: Discovery Laboratories, Inc. contracts with a laboratory at the (b) (4) (b) (4) to perform testing of KL₄ (lucinactant) surfactant drug product. The laboratory at (b) (4) generated raw data using a fetal rabbit biological activity test (FRBAT) and sent the data back to the sponsor for analyses. The laboratory at (b) (4) was inspected in December 2011. Since the sponsor performs the data analysis, interpretation, and report writing functions, an inspection was requested to confirm the integrity of the data submitted to the Agency to support the validation of Method DP-032.

Inspectional Findings: This was a directed GLP inspection requested by the Division of Pulmonary, Allergy, and Rheumatology Products. Deficiencies were observed during the inspection and a Form FDA 483 was issued (Attachment 1). Our evaluation of the inspectional findings and the firm's responses to the observations (Attachment 2) follow.

1) Failure of the firm to adequately document unexpected events. Specifically, lot T0002, Analyst 1, Run 2-1, Release testing conducted on 4/14/10 stated "Data not valid" rather than provide an explanation that the data from doe 82, birth order 7 was used instead of doe 82, birth order 8.

During release testing of lot T0002, Analyst 1, Run 2-1, the compliance data were incorrectly reported from doe 82, birth order 7 (Port #6) instead of doe 82, birth order 8 (Port #7). Both kits received test article but the compliance data from doe 82, birth order 7 (Port #6) correspond with release testing for lot T0002, Analyst 1, Run 3-1 rather than Run 2-1. The sponsor's documentation stated "Data not valid" rather than providing a description of the error and explaining that the incorrect compliance data were used in the analysis. The correct compliance data from doe 82, birth order 8 were ultimately used in the analysis and reported to the Agency. This had no impact on the validation of Method DP-032.

Firm's Response:

When the sponsor received the results for lot T0002, Analyst 1, Run 2-1, it was discovered that the data from Doe 82, birth order 7 was provided as the data for Doe 82, birth order 8. Since it is not possible to amend a data sheet once it is sent from (b)(4), the sponsor invalidated the data sheet and a new data sheet was requested from (b)(4). While it was acceptable for the sponsor to invalidate the incorrect data and replace it with the correct data, the rationale was not documented in the laboratory notebook.

The sponsor stated that they will amend standard operating procedures (SOPs): QC125, Maintenance and Review of Laboratory Notebooks; QC126, Quality Control Review and Approval of Analytical Test Results; and QA007, Quality Assurance Review and Approval of Analytical Test Results, and train all involved in the recording and quality assurance analysis of data to ensure that the rationale supporting invalidation of data is sufficiently documented in the laboratory notebook where the invalid data are recorded.

2) Failure of the firm to adequately follow Method DP-032, rev. 02. Specifically, Tier 2 testing was performed for lot T0002, Analyst 2, Test 2, Release testing even though the CV% for the three runs was less than 30%.

During release testing of lot T0002, Analyst 2, Test 2, the percent coefficient of variation was less than 30% for the three runs (Runs 2-1, 2-2, and 2-3). According to Method DP-032, rev. 2, Section 6.2.1, Tier 2 testing is to be performed for release testing if the CV >30%. However, the Analytical Test Results Report (ATRR) incorrectly stated "...% compliance greater than 546% Tier 2 required". Thus, Tier 2 testing was performed. The mean compliance value for Test 2, Tier 1 testing was 560.5% and exceeded the lower limit of 300% percent increase in compliance. Following Tier 2 testing, the mean compliance value for Test 2 was 486.5%. Although the results of Tier 1 rather than Tier 2 should have been reported to the Agency, it did not impact the validation of Method DP-032.

Firm's Response:

For Lot T0002, Analyst 2, Test 2, Release, the results were Out-of-Trend (OOT) but did not meet the sole criterion specific to release testing of having a CV >30% for the three (3) runs. When analytical methods employed by the sponsor do not have an embedded process to address OOT

results, an investigation is initiated in accordance with SOP QC002, Investigation of Non-Conforming and Aberrant Laboratory Results. In this specific instance, a retest would have been performed. However, this retest would have been part of an investigation, not a Tier 2 test as defined by Method DP-032, revision 2.

In the future, the sponsor will ensure that any release values outside of the boundary for the regression trend line will not go to Tier 2. All personnel involved in the recording and quality assurance analysis of data generated by the FRBAT will be trained on this observation, SOP QC002, and Method DP-032, to reinforce the process for determining an OOT result versus the requirements for Tier 2 testing. The training will be completed in March 2012.

3) Failure of the firm to consistently use the terms "Tier 2" and "Tier 3" as defined in Method DP-032, rev. 02. Specifically, Notebook A0463 incorrectly refers Test 2 as "Tier 2" for lot T0002, Analyst 1, Test 2 and Test 3 as "Tier 3" for lot T0002, Analyst 1, Test 3. Further, Supplement # 02 refers to N=6 as "Tier 2" and N=9 as "Tier 3".

Notebook A0463 for lot T0002, Analyst 1 refers to release testing of Test 2 (Runs 2-1, 2-2, and 2-3) as "Tier 2" and release testing of Test 3 (Runs 3-1, 3-2, and 3-3) as "Tier 3". Method DP-032, rev. 2, Section 6.2.1 defines Tier 2 and Tier 3 testing for OOT data assessments. However, notebook A0463 incorrectly uses the terms Tier 2 and Tier 3. Further, Supplement #02 to lot T0002, Analyst 1 release testing incorrectly refers to Tier 2 as the combined results of Tests 1 & 2 (N=6) and Tier 3 as the combined results of Tests 1, 2 & 3 (N=9). However, the correct compliance data were reported for the Agency for lot T0002, Analyst 1, Tests 1, 2, and 3 and the improper usage of Tier 2 and Tier 3 terminology in notebook A0463 and in supplement #02 did not impact the validation of Method DP-032.

Firm's Response:

The sponsor stated that early on during the validation exercise, there were instances where the second and the third Test of the triplicate testing (Test 2 ["N=6"] and Test 3 ["N=9"]) were mislabeled in the header of the laboratory notebook as Tier testing. The sample and run information recorded in the header of the N=3 data sheet were all found to be correct. In the instance cited in the observation, Analyst 1 completed three Tests of Lot T0002, yielding three reportable values to fulfill the requirement for triplicate testing. However, the notations in the laboratory notebook indicated that Test 2 was a Tier 2 test, and that Test 3 was a Tier 3 test.

The sponsor further stated that the results from Test 1, Test 2, and Test 3 performed on lot T0002 by Analyst 1 were appropriately imputed as three distinct reportable values from three Tests. Therefore, the mislabeled notebook headers cited in the observation did not change the outcome of the validation. All personnel involved in the quality assurance or analysis of data generated by the FRBAT will be retrained on Method DP-032 and good documentation practices in March 2012 to ensure that laboratory notebook pages are properly labeled going forward.

4) Failure of the firm to follow SOP QC-063, Section 7.1.7., stating that all testing for samples at the initial, one month, and two month time points be completed within 14 calendar days of the sample pull date. Specifically, lot T0002 was manufactured on 2/24/10 and Tier 2 testing for Analyst 2, Test 2 was performed on 4/12/10 and 4/13/10, exceeding the 14 calendar day requirement.

SOP QC-063, Section 7.1.7 states that “All testing for samples at the initial, one (1), and two (2) month time points, as per protocol, is to be completed within fourteen (14) calendar days of sample pull date, unless otherwise noted in the stability protocol.” However, the SOP does not allow for a revised timeline in the event that the run does not meet system suitability or Out-of-Trend assessments. Although lot T0002, Analyst 2, Test 2, release testing exceeded the 14 day limit due to Tier 2 testing, this had no impact on the validation of Method DP-032 since the Tier 1 compliance value (560.5%) and the Tier 2 compliance value (486.5%) exceeded the lower limit.

Firm’s Response:

The sponsor responded by stating that routine testing of T0002 was completed within 14 calendar days (i.e., the FRBAT yielded at least one reportable release value). Triplicate testing by two different analysts, inclusive of a Tier 2 test, was completed within a 6 week time frame. The results of the testing over this time frame are reported in the analysis of intermediate precision in METHVAL-52 (Section 4.3.2). The overall CV% for intermediate precision was 6.0%, below the specified limit, also demonstrating that all values over the 6 week testing time frame were consistent. Therefore, the timing of the testing in this instance did not affect the outcome of the validation of Method DP-032.

5) Failure of the firm to provide a rationale for repeating data, which is not in accordance with Method DP-032. Specifically, lot T9002, 15C, 6 weeks, runs 1-1 and 3-1 were initially performed on 3/2/10 and 3/3/10 and repeated on 3/9/10 and 3/10/10 without adequate justification.

Six week stability testing at 15C for Lot T9002, Runs 1-1 and 3-1 was performed on 3/2/10 and 3/3/10. The data were invalidated and subsequently repeated on 3/9/10 and 3/10/10. The documentation on the data sheets in laboratory notebook A0461 state “Data Invalid” and refer to INV-10-007 (Investigation Report INV-10-007). However, investigation INV-10-007 is unrelated to lot T9002 Runs 1-1 and 3-1 and fails to provide further information. Although no explanation was given by the sponsor for rejecting the data and subsequently repeating Runs 1-1 and 3-1, repeating Runs 1-1 and 3-1 did not impact the validation of Method DP-032. In the future, the sponsor should follow their criteria to determine when runs should be repeated.

Firm’s Response:

The sponsor stated that repeat testing using Method DP-032 is permitted if the data from a test are invalidated or if the results meet criteria for Tier testing. In the example cited in the observation, the data were reviewed and marked as "Data Invalid" on the data sheet without an explanation justifying the invalidation of the data. Both runs satisfied the system suitability

criteria. The sponsor determined that the resultant linear degradation for stability would not have been appreciably different if the original compliance values were used from what was reported in the validation report for Method DP-032. Thus, the repeat testing did not affect the validation of Method DP-032.

6) Failure to comply with 21 CFR Part 58 for a study stated to be in compliance with the Good Laboratory Practice Regulations, specifically,

a. Failure of the firm to assign a Study Director to Method DP-032, rev. 2.

Firm's Response:

The sponsor stated that (b) (4) was responsible for the technical conduct of the study, was the lead individual at (b) (4) responsible for documentation and reporting results, reviewed and approved the validation protocol, assured that the test systems were as specified in the protocol, and assured that the protocol was executed as written; also that these responsibilities are consistent with the critical aspects of a Study Director. However, (b) (4) did not have overall responsibility for the interpretation, analysis, documentation and reporting of results and did not represent the single point of study control as required by 21 CFR 58.33.

b. Failure of the firm to establish a Quality Assurance Unit responsible for monitoring the conduct of Method DP-032, Rev. 2.

Firm's Response:

The sponsor stated that they had a Quality Operations Department that was responsible for monitoring the conduct of the validation of Method DP-032, revision 2 comprised of the Quality Assurance (QA) personnel and facilities at Discovery in Warrington, PA as well as an employee and a contractor local to the laboratory at (b) (4). However, the Quality Assurance oversight provided by the sponsor failed to submit to status reports on each study, to note any problems and corrective actions taken and determine that no deviations from approved protocols or SOPs were made without proper authorization and documentation.

c. Failure of the firm to maintain a Master Schedule of all non-clinical laboratory studies conducted at the testing facility, indexed by test article and containing the test system, nature of study, date study initiated, current status of each study, identity of the sponsor, and the name of the study director.

Firm's Response:

The response stated that the laboratory at (b) (4) in addition to the sponsor maintains a Master Schedule of all laboratory activities and the components of this schedule are consistent with the critical aspects of a Master Schedule. The Master Schedule is indexed by test article, specifically by Surfaxin lot number, and included the test number for that lot, the shelf age of the sample to be tested, the anticipated or actual start date of the testing, and the actual or anticipated end date of the testing. Since the (b) (4) laboratory performs the test exclusively for the sponsor, the test

system, identity of the sponsor, and the name of the Study Director is inferred. However, the Master Schedule that the sponsor and the laboratory at (b)(4) provided to the investigators did not include all the information required in 21 CFR 58.35(b)(1).

Discussion Items:

- The sponsor needs to improve the Quality Assurance operations by providing training of method DP032 and relevant SOPs. As an example, the positive controls for lot T8006, Runs 2-2 and 3-2 failed to meet system suitability but were submitted by the laboratory at (b)(4) and accepted by the sponsor’s Quality Assurance Unit.

Recommendations:

- The data supporting the validation of Method DP-032 were found to be acceptable.
- The sponsor needs to provide further training to staff to ensure that Method DP-032 and SOPs are followed in the future
- Since the firm does not currently perform GLP studies, there is no need to schedule a future surveillance inspection.
- Recommended HQ classification: Voluntary Action Indicated (VAI).

Charles R. Bonapace, Pharm.D.
Acting GLP Branch Chief

William H. Taylor, Ph.D.
Acting Division Director Concurrence:

Concur: _____ Date: _____

Nonconcurrency: _____ Date: _____
(see attached supervisory memorandum)

Date Assigned: 1/27/2012
EI Dates: 2/21-24/2012

District Office: PHI-DO
FEI: 3004898726
FDA Investigators: James P. McEvoy, PHI-DO

Inspection Type: Routine Surveillance Directed
FDA-483 Issued: No Yes
Letter Issued: None (CDER) Untitled Letter
 Warning Letter Rejection of Study

Date EIR Received OSI:
Date EIR Received by Reviewer:
1st Draft Review Completed: 3/1/2012

FEI: 3004898726
FACTS: 1378859

Inspection Conclusion: VAI
District Decision:
Final HQ Classification: VAI

cc:
CDER DSI PM TRACK
DPARP/Ramsey, Robison, Pei
PHI-DO/McEvoy/Campbell/Tammariello
OSI/DBEGLPC/Taylor/Matthews/Dejernet/Bonapace/CF
Draft: CRB 3/1/2012
Edits: WHT 3/1/2012
DSI File: GLP0821
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Attachment #1

Form FDA 483

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

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

/s/

CHARLES R BONAPACE
03/02/2012

WILLIAM H TAYLOR
03/02/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 21746	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Surfaxin Established/Proper Name: lucinactant Dosage Form: Intratracheal Suspension Strengths: 30mg/ml		
Applicant: Discovery		
Date of Receipt: September 6, 2011		
PDUFA Goal Date: March 6, 2012		Action Goal Date (if different):
Proposed Indication(s): Prevention of Respiratory Distress Syndrome in Premature Infants		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature referencing surfactant	Nonclinical data

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor is using proposed literature (a nonclinical study demonstrating the biological activity of lucinactant in a lamb model of neonatal respiratory distress syndrome) as a bridge to demonstrate comparable biological activity for the proposed marketed product. The nonclinical published study utilized the same drug product lots which were used in the pivotal clinical trial. Because at the time the pivotal study was conducted a valid bioassay to detect surfactant activity had not been developed, the nonclinical study “bridges” the activity of the product used in clinical studies to that of the proposed marketed product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

NO Yes

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

NO Yes

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).
lucinactant

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

NO

Yes



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

NO Yes

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

ANGELA H RAMSEY
03/02/2012

MEMORANDUM

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

DATE: March 1, 2012

TO: Discovery Laboratories

THROUGH: **Russell Clayton**

FROM: Angela Ramsey

SUBJECT: **Clarify issues related to analytical testing sites**

APPLICATION/DRUG: **NDA 21-746/Surfaxin (lucinactant) Intratracheal Suspension**

The Division held a teleconference with Discovery Laboratories to discuss future plans of transferring testing site responsibilities to (b) (4). The Division requested a commitment from Discovery that the method validation transfer to (b) (4) will be consistent with the Warrington, PA site. Discovery anticipates the transfer to (b) (4) within 6- 12 months and confirmed that there will not be any changes to the method validation. Discovery stated that Warrington, PA personnel will be present to validate and make sure consistency is maintained during the transfer.

Discovery has agreed to submit a summarized plan to transfer quality assurance and analysis testing responsibilities to (b) (4) by tomorrow.

Discovery also agreed to submit a PAS once the testing site has been transferred to (b) (4).

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/s/

ANGELA H RAMSEY
03/01/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: February 10, 2012

Reviewer(s): Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Deputy Director: Kellie Taylor, PharmD, MPH
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Surfaxin (Lucinactant) Intratracheal Suspension, 8.5 mL

Application Type/Number: NDA 021746

Applicant: Discovery Laboratories

OSE RCM #: 2011-4084

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Surfaxin (lucinactant) intratracheal suspension, 8.5 mL for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

The application for Surfaxin (NDA 21746) received an “Approvable” action on April 23, 2008 due to Chemistry, Manufacturing, and Controls (CMC) deficiencies and received a Complete Response (CR) Letter on April 17, 2009. Subsequently, the applicant submitted a resubmission in response to the deficiencies outlined in the April 17, 2009 CR Letter, dated September 2, 2011. In this resubmission, the applicant requested a review of the container label, carton labeling, and package insert for Surfaxin.

1.2 PRODUCT INFORMATION

The following product information is provided in the September 2, 2011 submission.

- Active Ingredient: Lucinactant
- Indication of Use: Prevention of Respiratory Distress Syndrome (RDS) in Premature Infants at High Risk for RDS.
- Route of Administration: Intratracheal
- Dosage Form: Suspension
- Strength: Each mL contains 30 mg phospholipids, 0.863 mg peptide and 4.05 mg palmitic acid
- Dose: 5.8 mL/kg of birth weight
- How Supplied: Sterile, single-use, rubber-stoppered, clear glass vials containing 8.5 mL of white suspension. One vial per carton.
- Storage: Store in a refrigerator at 2° to 8°C (36° to 46°F) and protect from light until ready for use. Do not freeze.
- Intended pronunciation: Ser-‘faks-en

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 2, 2011 (Appendix A)
- Carton Labeling submitted September 2, 2011 (Appendix B)
- Insert Labeling submitted September 2, 2011
- Previous DMEPA Review #04-0194-1 dated October 5, 2005

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication errors. We recommend the following be implemented prior to approval of this NDA.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

A. GENERAL COMMENTS (CONTAINER LABEL AND CARTON LABELING)

1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast and other printing features as stated in 21 CFR 201.10 (g)(2).
2. Revise the statement “For Intratracheal Administration Only” to read “For Intratracheal Use Only”.
3. The statements “For Intratracheal Use Only” and “Not for Injection” should be bolded or color blocked to increase their prominence since the packaging configuration can be confused for other routes of administration (e.g. Intrathecal).
4. Revise the statement “Single Use Vial” to read “Single use vial. Discard unused portion.” You may present these statements on two lines. To achieve this on the container label we recommend relocating the statement “Sterile Suspension” to the side panel to the location where the statement “Discard any unused portion” currently resides.

B. PACKAGE INSERT LABELING

DMEPA’s recommendations on the package insert labeling were discussed during the labeling meeting and incorporated into the draft labeling submitted to the applicant.

1. In Dosage and Administration section, the dosing statement was revised to read “The recommended dose..” instead of “Each dose...”
2. In Dosage and Administration section, the dosing statement (b) (4) was removed since the product is dosed in mL.
3. (b) (4)

DMEPA recommended deleting the trailing zero in Table 1. Dosing Chart (i.e. 7.0) as this is considered to be an error-prone designation. This recommendation was discussed during the December 7, 2011 mid-cycle and labeling meeting. The review division did not agree because this statement is necessary to show precision in the measurement of the dose. In addition, they stated that it would not be a source of confusion due to the specific setting of use. This product is usually ordered before birth so that they are available in the delivery room/NICU when the baby is delivered or arrives.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

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

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/s/

REASOL AGUSTIN
02/10/2012

CARLOS M MENA-GRILLASCA
02/10/2012

KELLIE A TAYLOR
02/10/2012

CAROL A HOLQUIST
02/10/2012

MEMORANDUM

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

DATE: January 27, 2012

TO: Director, Investigations Branch
Philadelphia District Office
U.S. Customhouse, Room 900
2nd and Chestnut Streets
Philadelphia, PA 19106

From: Charles R. Bonapace, Pharm.D. _____
Acting Chief, Good Laboratory Practice (GLP) Branch
Division of Bioequivalence & GLP Compliance
Office of Scientific Investigations (OSI)
Office of Compliance (OC)

SUBJECT: FY 2012, **PDUFA GLP Directed Inspection**, Bioresearch
Monitoring, Human Drugs, CP 7348.808

This memo requests that you arrange for a GLP Directed inspection of the following facility:

FACILITY: Discovery Laboratories, Inc.
ADDRESS: 2600 Kelly Road, Suite 100
Warrington, PA
FEI: 3004898726

Preannouncement of our intent to inspect should not be made.
We request that this inspection be completed by February 24, 2012. An OSI scientist with specialized knowledge will participate in the inspection to provide scientific and technical expertise. Please contact OSI to coordinate the inspection schedule.

The Division of Pulmonary, Allergy, and Rheumatology Products requests the following study be inspected and evaluated for data integrity. The drug used in the study, SURFAXIN[®] (lucinactant) will be used as a life saving therapy in pre-mature infants at high risk for Respiratory Distress Syndrome. This study is pivotal to support approval of NDA 21-746.

NDA: 21-746

Sponsor/Test Facility: Discovery Laboratories, Inc.

Report Number: METHVAL-52: Analytical & Technical Support
Validation Report

Method Number: DP-032, revision 02

Protocol Numbers: VALPROT-72, Rev 00, VALPROT-85, Rev 00, and VALPROT-86, Rev 00

Protocol Title: Report of the Validation of the Analytical Test Method DP-032 "*In Vivo Biological Activity Test for KL₄ Surfactant Drug Product*" (VALPROT-72, Rev 00)

Analytical & Technical Support Validation Report Date: 9/2/2011

Discovery Laboratories, Inc. was involved in data generation, processing, evaluation and interpretation and reporting of the validation of the fetal rabbit bioassay used to test the biological activity of lung surfactant in SURFAXIN[®] (lucinactant) intratracheal suspension.

All pertinent items related to Report METHVAL-52 should be audited, particularly the sponsor's data analysis of the accuracy, precision, specificity, and linearity of Method DP-032. The protocol and actual study conduct, QAU monitoring, maintenance and calibration of pertinent equipment, and the archives should be examined. The SOPs for the various procedures need to be scrutinized. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Applicable exhibits (e.g., SOPs, raw data sheets) should be collected for all findings to assess the impact of the findings.

In addition, a copy of the master schedule, encompassing the facility's workload in 2011-2012 should be collected and exhibited in the EIR. As required by 21 CFR 58.35(b)(1), the master schedule should be indexed by test article, test system, nature of study, date study initiated, current status, sponsor and study director. If the master schedule uses coded entries, the key for the code should also be collected.

The following issues must be addressed during the inspection and discussed in the EIR:

- What percentage of the facility's total workload is subject to Part 58? What percentage of the facility's GLP workload is related to human drugs?
- Does the facility outsource any study phases, e.g., analysis of dosing formulations and histopathologic evaluations? Document how QAU oversight is assured for the outsourced phases. Does the final report identify the facility that conducted the outsourced phases? Please collect and exhibit in the EIR a list of all firms used for outsourced phases.

- Did the study director sign and date protocol amendments on or before the day when procedures were actually changed?
- Were the results of test article characterization and dosing formulation analyses reported to the study director and included in the final report?
- Were signed and dated contributing scientists' reports attached to the final report? Please determine and document if the study director prepared the final report without signed and dated contributing scientists' reports, as applicable to the study under audit.

Headquarters Contact Person: Abhijit Raha, Ph.D.
TELEPHONE: 301-796-3708
EMAIL: abhijit.raha@fda.hhs.gov

cc:

email using DARRTS

HFR-CE1515/Daniel Tammariello (BIMO)
HFR-CE150/Karyn Campbell (DIB)
ORA/ORO/DDFI/DOB/Caphart
OSI/DBEGLPC/Taylor/Salewski/Bonapace/Matthews/Dejernet/Raha/CF
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/s/

ABHIJIT RAHA
01/27/2012

CHARLES R BONAPACE
01/27/2012

DSI CONSULT Request for Nonclinical Inspections
--

DATE: January 26, 2012

TO: Charles Bonapace, Team Leader
Division of Scientific Investigations
Office of Compliance

GLP Team, GLP and Bioequivalence Investigations Branch
Attn: Jacqueline A. O'Shaughnessy, Ph.D., Acting GLP Team Leader

THROUGH: Luqi Pei, Senior Pharmacologist, Division of Pulmonary, Allergy and
Rheumatoid Drug Products (DPARP), Office of New Drugs and

Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader, DPARP

FROM: Angela Ramsey, Senior Regulatory Project Manager, DPARP

SUBJECT: Request for Nonclinical Site Inspections
NDA 21-746
Surfaxin (lucinactant) Intratracheal Suspension
Discovery Laboratories

Study/Site Identification:

The following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study # and brief title	Testing Facility (name, address, contact information)	Site Description (e.g., in-life facility, bioanalytical lab, histopathology evaluation)
Methval 52: Analytical and Technical Support Validation Report	Discovery Laboratories ^a 2600 Kelly Road, Suite 100 Warrington, PA FEI# 3004531525	Data generating, processing, summary, interpretation, evaluation, and reporting of fetal rabbit bioassay in Report Methval 52

Report for Validation
of Analytical Test
Method DP-032 "in
Vivo Biological
Activity Test for KL₄



Fetal Rabbit Biological
Activity Testing (FRBAT)

-
- a. Please note that this site was inspected on Dec. 19 - 24, 2011 by Anita Michael. The site was listed in EES with FEI# 3004898726, however since then the responsibilities of the site were changed as described in NDA Amendment dated Jan 23, 2012.
 - b. This site was inspected in for GLP Compliance by Dr. Charles Bonapace. A 483 Form was issued. See a pharmacologist review of GLP EIR (CP 7348.808) completed by Dr. Charles Bonapace on January 13, 2012 for additional information.

The study report and data listings can be found at: N/A.

Domestic/International Inspections:

(Please note: International inspections require sign-off by the OND Division Director.)

We have requested an inspection because:

There is a lack of domestic data that solely supports approval.

 X Other (please explain): This is a for-cause request. This inspection is needed to complete a GLP inspection that the Agency initiated in December 2011. The GLP inspection is to validate some pivotal nonclinical data in support of the approval of the September 6, 2011 resubmission in NDA 21-746. See the Additional Comments section (below) for more information.

Additional Comments: (As needed)

The Agency is evaluating the integrity of two nonclinical study reports (Report Methval 52 and SOP DP-32, 02) submitted in NDA 21-746 on September 2, 2011. As a part of the process, the Agency conducted a GLP inspection of one of the two sites involved in generating the reports in December 2011. The other site must also be inspected to complete the GLP inspection process. The to-be-inspected site was not inspected previously because the reports failed to identify it.

The Agency's recent inspection in December 2011 found that two sites are involved in generating the reports of interest. The sites are located in and Pennsylvania (2600 Kelly Road, Suite 100 Warrington, PA, FEI# 3004531525), respectively. The Agency inspected the site only. The inspection revealed that the Pennsylvania site was also a major contributor of the reports. Briefly, the site was responsible for generating the raw data. The Pennsylvania site was responsible for data analysis, integration, evaluation and report writing. Both the and Pennsylvania sites should be inspected for a complete and thorough GLP inspection.

Discovery (the applicant) has submitted several versions of Methval 52 and Method DP-32. We are questioning the data integrity among the versions of respective individual reports and data integrity between Methval 52 and Method DP-32. Please check the following versions because they are of most interest to us at the present time:

Report	Version	Effective Date	Submission Date
Methval 52	02	Sep. 2, 2011	Sep. 2, 2011
	03	Jan. 16, 2012	Jan. 16, 2012
Method DP-32	02	Nov. 2, 2009	Mar 5, 2010
	05	Jan. 16, 2012	Jan. 16, 2012

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **February 15, 2012**. We intend to issue an action letter on this application by March 6, 2012.

Should you require any additional information, please contact Angela Ramsey, Senior Regulatory Project Manager at 301-796-2284.

Concurrence: (As needed)

Timothy Robison, Ph.D., Pharmacology/Toxicology Supervisor

Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer

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/s/

ANGELA H RAMSEY
01/26/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 21-746

Name of Drug: Surfaxin (lucinaquant) Intratracheal Suspension

Applicant: Discovery Laboratories

Labeling Reviewed

Submission Date: September 2, 2011

Receipt Date: September 6, 2011

Background and Summary Description

Discovery submitted a resubmission dated, September 2, 2011, in response to the Complete Response Action dated, April 17, 2009 for Surfaxin (lucinaquant) Intratracheal Suspension for the prevention of respiratory distress syndrome in premature infants.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. There were no labeling deficiencies identified with the SRPI, but the following labeling issues pertain to the Dosage and Administration section and Dosage Forms and Strengths section were identified:

Use "per" instead of "slash mark" to separate doses

Conclusions/Recommendations.

All labeling deficiencies identified in this review will be conveyed to the applicant in an advice letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by January 31, 2012. The resubmitted labeling will be used for further labeling discussions.

Angela Ramsey
Regulatory Project Manager

January 13, 2012
Date

Sandy Barnes
Chief, Project Management Staff

January 23, 2012
Date

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/s/

ANGELA H RAMSEY
01/24/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 13, 2012

To: Angela Ramsey, Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Division of Professional Promotion (DPP), Office of Prescription
Drug Promotion (OPDP)

CC: Lisa Hubbard, Group Leader, DPP, OPDP
Robyn Tyler, Group Leader, Division of Direct-to-Consumer
Promotion (DDTCP), OPDP
Matthew Falter, Regulatory Review Officer, DDTCP, OPDP
Olga Salis, Project Manager, OPDP

Subject: NDA 021746
OPDP labeling comments for Surfaxin (lucinactant) Intratracheal
Suspension

OPDP has reviewed the proposed Package Insert (PI) and Carton and Container Labeling for Surfaxin (lucinactant) Intratracheal Suspension (Surfaxin) submitted for consult on November 15, 2011, and offers the following comments.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "Surfaxin FDA DRAFT Labeling 01-05-2012_PLR.docx" that was sent via e-mail from DPARP to OPDP on January 6, 2012. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed carton and container labeling submitted by the sponsor on September 2, 2011, and located in the EDR at:

- <\\cdsesub4\NONECTD\NDA021746\4925023\Labeling>

OPDP has no comments at this time on the proposed carton and container labeling.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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

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/s/

ROBERTA T SZYDLO
01/13/2012

MEMORANDUM

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

DATE: October 27, 2011

TO: Director, Investigations Branch

[REDACTED] (b) (4)

From: Charles R. Bonapace, Pharm.D. _____
Acting Team Leader (GLP)
Division of Bioequivalence & GLP Compliance
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **PDUFA GLP Directed and Surveillance
Inspection**, Bioresearch Monitoring, Human Drugs, CP
7348.808

This memo requests that you arrange for a GLP Directed and Surveillance inspection of the following facility:

FACILITY: [REDACTED] (b) (4)
ADDRESS: [REDACTED]
FEI: [REDACTED]

Preannouncement of our intent to inspect should not be made.
We request that this inspection be completed by January 14, 2012. An OSI scientist with specialized knowledge will participate in the inspection to provide scientific and technical expertise. Please contact OSI to coordinate the inspection schedule.

The Division of Pulmonary, Allergy and Rheumatology Products requests the following study be inspected for data integrity. The drug used in the study, SURFAXIN® (lucinactant), will be used as a life saving therapy in pre-mature infants at high risk for Respiratory Distress Syndrome. This study is pivotal to support an NDA approval.

NDA: 21-746

Sponsor: Discovery Laboratories

Study Title: Report for the Validation of the Analytical Test Method DP-032 "In Vivo Biological Activity Test for KL₄ Surfactant Drug Product"

If available, a copy of the master schedule, encompassing the facility's workload should be collected and exhibited in the EIR. As required by 58.35 (b) (1), the master schedule should be indexed by test article, test system, nature of study, date initiated, current status, sponsor, and study director. If the master schedule uses coded entries, the key for the code should be also collected.

All pertinent items related to the study should be examined and the sponsor's data should be audited. The protocol and actual study conduct, QAU monitoring, maintenance and calibration of pertinent equipment, and the archives should be examined. The SOPs for the various procedures need to be scrutinized. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Applicable exhibits (e.g., SOPs, raw data sheets) should be collected for all findings to assess the impact of the findings.

The following issues must be addressed during the inspection and discussed in the EIR:

- What percentage of the facility's total workload is subject to Part 58? What percentage of the facility's GLP workload is related to human drugs?
- Does the facility outsource any study phases, e.g., analysis of dosing formulations and histopathologic evaluations? Document how QAU oversight is assured for the outsourced phases. Does the final report identify the facility that conducted the outsourced phases? Please collect and exhibit in the EIR a list of all firms used for outsourced phases.
- Did the study director sign and date protocol amendments on or before the day when procedures were actually changed?
- Were the results of test article characterization and dosing formulation analyses reported to the study director and included in the final report?
- Were signed and dated contributing scientists' reports attached to the final report? Please determine and document if the study director prepared the final report without signed and dated contributing scientists' reports, as applicable to the study under audit.
- If applicable, have deficiencies identified by DSI from the previous inspection been corrected? Have the corrective actions prevented recurrence of the deficiencies?

Headquarters Contact Person: Abhijit Raha, Ph.D.
301-796-3708
abhijit.raha@fda.hhs.gov

cc:

HFR-PA2535/Allen Hall(BIMO)
HFR-PA252/Monica Maxwell(DIB)
ORA/ORO/DDFI/DOB/Capron
OSI/GLPBB/Bonapace/ChenZ/Raha/Ead/CF
Draft: ChenZ 10/24/2011; 10/27/2011
Edit: AR 10/24,27/2011; ChenZ 10/24/2011; CRB 10/24/2011
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/s/

ABHIJIT RAHA
10/27/2011

ZHOU CHEN
10/27/2011

CHARLES R BONAPACE
10/27/2011

DSI CONSULT
Request for Nonclinical Inspections

DATE: October 12, 2011

TO: Charles Bonapace, Team Leader
 Division of Scientific Investigations
 Office of Compliance

GLP Team, GLP and Bioequivalence Investigations Branch
 Attn: Jacqueline A. O'Shaughnessy, Ph.D., Acting GLP Team Leader

THROUGH: Timothy Robison, Ph.D., Team Leader, and Luqi Pei, Ph.D., Reviewer,
 Pharmacology/Toxicology, Division of Pulmonary, Allergy, and Rheumatology Products

FROM: Angela Ramsey, Senior Regulatory Project Manager, Division of Pulmonary,
 Allergy, and Rheumatology Products

SUBJECT: Request for Nonclinical Site Inspections
 NDA 21-746
 Surfaxin (lucinactant) Intratracheal Suspension
 Discovery Laboratories

Study/Site Identification:

The following studies/sites pivotal to approval of NDA 21-746 (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study # and brief title	Testing Facility (name, address, contact information)	Site Description (e.g., in-life facility, bioanalytical lab, histopathology evaluation)
Report for Validation of Analytical Test Method DP-032 "in Vivo Biological Activity Test for KL ₄ Surfactant Drug Product	(b) (4)	This site conducts the Fetal Rabbit Biological Activity Testing (FRBAT).

The portion of the NDA resubmission describing the FRBAT assay was a paper submission.

Domestic/International Inspections:

(Please note: International inspections require sign-off by the OND Division Director.)

We have requested an inspection because:

There is a lack of domestic data that solely supports approval.

Other (please explain): This is a domestic inspection. The animal model is of interest because it is the assay for assessing efficacy specifications of Surfaxin, a drug that will be used as a life saving therapy in pre-mature infants. We request the inspection to ensure that the data generated from the assay meets current GLP standards. With reference to the recent NDA resubmission, please verify the integrity of this data (there have been significant problems with the assay in past submissions; a preliminary review of data in the recent resubmission suggests improvement of assay and data generated from it).

Additional Comments: (As needed)

An inspection was done during (b) (4), and Form 483 was issued. (b) (4) recommended approval in 2004 and also in Dec 2007, based on "file review". Our current request for EER update is pending. The site does not have CFN or FEI number assigned.

A protocol of the FRBAT and summary data produced from the protocol are attached.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **December 30, 2011**. We intend to issue an action letter on this application by March 6, 2012.

Should you require any additional information, please contact Angela Ramsey, Senior Regulatory Project Manager at 301-796-2284.

Concurrence: (As needed)

Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader

Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer

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/s/

ANGELA H RAMSEY
10/12/2011

**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

MEMORANDUM

****Pre-Decisional Agency Information****

Date: February 27, 2008

To: Lori Garcia, R.Ph. – Regulatory Project Manager
Division of Pulmonary and Allergy Products (DPAP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC labeling comments for Surfaxin (lucinactant) Intratracheal
Suspension (Surfaxin)
NDA 21-746

DDMAC has reviewed the revised proposed product labeling (PI) and proposed carton and container labeling for Surfaxin submitted for consult on February 25, 2008. We acknowledge that the sponsor's October 31, 2007, submission is a complete response to the deficiencies listed in the Approvable letter dated March 31, 2006.

Reference is made to DDMAC's comments dated March 14, 2006 (also containing comments dated February 1, 2006) on the initial proposed PI and proposed carton and container labeling dated July 15, 2005.

We offer the following comments.

PI

(b) (4)

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/s/

Michelle Safarik
2/27/2008 02:20:39 PM
DDMAC REVIEWER

ADRA Rev #2 of Action Package for NDA 21-746, Surfaxin (lucinactant) Intratracheal Suspension

Lucinactant is USAN for the mixture: sinapultide (a synthetic peptide), colfosceril palmitate (dipalmitoylphosphatidylcholine, DPPC) (a synthetic phospholipid), palmitoyloleaylphosphatidyl glycerol, sodium salt (POPG), (a synthetic phospholipid), and palmitic acid (a fatty acid)

Reviewer: Lee Ripper, HFD-102

Date received: March 20, 2006

Date of review: March 21 *and* 31, 2006

Date original NDA received: April 13, 2004

UF goal date: April 6, 2006

ACTION DATE: April 4, 2006

Proposed Indication: Px of RDS in premature infants.

Action type: AE

RPM: Christine Yu

Drug Classification: 1SV
505(b)(1) application

Patent Info on form FDA 3542a: Received

Debarment Certification: AC

Safety Update: 9/30/04, MOR page 87. Also 3/10/06 MOR

Clinical Inspection Summary: 4 sites inspected, data appear to be AC, 1/5/05.

ODS/DMETS Review of Proprietary Name: DMETS does not recommend use of name Surfaxin, 11/8/04 and 3/1/06. 5/25/04 MOR found proprietary name not acceptable. 1/14/05 TL review, 2/8/05 DD, and 2/9/05 OD reviews found proprietary name acceptable.

DSRCS Review of PPI: No PPI

DDMAC Review: DDMAC finds name Surfaxin AC per DMETS reviews.

EA: CMC #1, page 53: categorical exclusion

EER: A withhold recommendation was signed 2/5/06. All sites acceptable except for Discovery (formerly Laureate) in Totowa which was assigned to IB for inspection 2/27/06. It's not clear from EES if this facility was inspected during the current review cycle and, if so, why another inspection was assigned at this. RPM is pursuing this question with DMPQ and the reviewing chemist.

Financial Disclosure: AC

CMC section to Chi-Wan Chen, 3/22/06. *Review signed 3/30/06.*

P/T section not circulated to Ken Hastings. His only comment in the first review cycle had to do with labeling. The pertinent labeling section was revised to read as requested in our 2005 action letter. 3/23/06: *Dr. Hastings confirmed that he did not need to see the package this review cycle.*

1. EER: Was the Totowa facility inspected during this review cycle? 3/31/06: *Inspection ongoing, to be completed early next week; withhold recommendation anticipated; deficiency added to letter.*

2. Do any DMF deficiency letters need to issue before the NDA action letter issues? It's not clear from the CMC review whether letters are needed for DMFs [REDACTED] ^{(b)(4)}. 3/31/06: *One letter issued and Art Shaw has completed the draft review on the other DMF. Letter expected to issue today.*

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/s/

Leah Ripper
3/31/2006 10:59:47 AM
CSO

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: February 1, 2006

To: Christine Yu, RPh, Regulatory Project Manager
Division of Pulmonary and Allergy Products

From: Michelle Safarik, PA-C, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: NDA 21-746
DDMAC labeling comments for Surfaxin (lucinactant) Intratracheal Suspension

Per your consult request dated October 31, 2005, DDMAC has reviewed the proposed product labeling (PI), proposed carton label, proposed vial label, and proposed logo for Surfaxin, and we offer the following comments.

PI



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/s/

Michelle Safarik
3/14/2006 10:56:25 AM
DDMAC REVIEWER

ADRA Rev #1 of Action Package for NDA 21-746, Surfaxin (lucinaquant) Intratracheal Suspension

Lucinaquant is USAN for the mixture: sinapultide (a synthetic peptide), colfosceril palmitate (dipalmitoylphosphatidylcholine, DPPC) (a synthetic phospholipid), palmitoyloleaylphosphatidyl glycerol, sodium salt (POPG), (a synthetic phospholipid), and palmitic acid (a fatty acid)

Reviewer: Lee Ripper, HFD-102

Date received: January 26, 2005

Date of review: February 2, 2005

Date original NDA received: April 13, 2004

UF goal date: February 13, 2005

ACTION DATE: February 11, 2005

Proposed Indication: Px of RDS in premature infants.

Action type: AE

RPM: Christine Yu

Drug Classification: 1SV

505(b)(1) application

Patent Info on form FDA 3542a: Received

Debarment Certification: AC

Safety Update: 9/30/04, MOR page 87.

Clinical Inspection Summary: 4 sites inspected, data appear to be AC, 1/5/05.

ODS/DMETS Review of Proprietary Name: DMETS does not recommend use of name Surfaxin, 11/8/04. HFD-170 DD and medical TL find the name AC; MOR did not find name AC.

DSRCS Review of PPI: No PPI

DDMAC Review: DDMAC finds name Surfaxin AC per DMETS review.

EA: CMC #1, page 53: categorical exclusion

EER: As of 2/1/05, EER had not been signed off by DMPQ. Three facilities were found to be UN by their district offices.

Financial Disclosure: AC

CMC section to Eric Duffy, 1/28/05

P/T section to Ken Hastings, 2/2/05

1. EER is pending.
2. A number of DMFs were found to be deficient. All DMF deficiency letters need to issue before the NDA action letter issues.

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/s/

Leah Ripper
2/8/05 05:45:39 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-746 Supplement type N/A (i.e., SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8) # _____

Trade Name: Surfaxin Intratracheal Suspension
Generic Name: lucinactant
Strengths: 30 mg phospholipids and 0.8 mg peptide/ml, 8 ml single use vial

Applicant: Discovery Laboratories, Inc.

Date of Application: 13 April 2004
Date of Receipt: 13 April 2004
Date clock started after UN:
Date of Filing Meeting: 10 May 2004
Filing Date: 12 June 2004
Action Goal Date (optional): 14 Jan 2005 User Fee Goal Date: 13 Feb 2005

Indication(s) requested: prevention of respiratory distress syndrome (RDS)

Type of Original NDA: (b)(1) ✓ (b)(2) _____

OR

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ✓ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) Orphan

User Fee Status: Paid _____ Exempt (orphan, government) Orphan
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # N/A
Clinical data? YES ✓ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

If yes, explain: YES NO

Does another drug have orphan drug exclusivity for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? *Datasets, CRFs*

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES NO
- Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ years NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
“*[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.*” Applicant may not use wording such as “To the best of my knowledge”

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 10, 2004

BACKGROUND:

Discovery Laboratories, Inc. is pursuing approval of Surfaxin (lucinactant), a synthetic surfactant for prevention of RDS in premature infants. Surfaxin has been designated as an orphan drug and is categorized as a NME. The applicant has conducted one international pivotal trial, a superiority trial against Exosurf with Survanta included as a reference arm, to support approval for Surfaxin. There are three surfactants approved and marketed in the U.S. - Survanta (bovine), Infasurf (bovine) and Curosurf (porcine). Exosurf (synthetic) is still approved but not marketed in the U.S.

ATTENDEES:

Eugenia Nashed, Rik Lostritto
Huiqing Hao, Joe Sun
Tayo Fadiran
Mahboob Sobhan, Ed Nevius
Harry Gunkel, Peter Starke, Eugene Sullivan
Badrul Chowdhury
Robert Meyer, ODE II
Ele Ibara-Pratt, DSI

ASSIGNED REVIEWERS:

Discipline

Medical:
Secondary Medical:
Statistical:
Pharmacology:

Statistical Pharmacology:
Chemistry:

Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
Regulatory Project Management:
Other Consults:

Reviewer

J Harry Gunkel
Peter Starke
Sue-Jane Wang
Huiqing Hao
Joseph Sun

Eugenia Nashed, Suong Tran
Rik Lostritto

Emmanuel Fadiran
Pawar, Vinayak
Ibarra-Pratt, Ele
Christine Yu

Per reviewers, are all parts in English or English translation?
If no, explain:

YES

NO

CLINICAL

FILE

REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY NA FILE _____ REFUSE TO FILE _____

STATISTICS FILE REFUSE TO FILE _____

BIOPHARMACEUTICS FILE REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
 Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

 Christine Yu, R.Ph., Regulatory Project Manager, HFD-570
 Concurrence: S Barnes/ 21 Jan 2005

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/s/

Christine Yu
1/26/05 09:53:18 AM
CSO

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 3, 2005

TO: Christine Yu, Regulatory Project Manager
John Gunkel, M.D., Medical Officer, Clinical Reviewer
Division of Pulmonary & Allergy Drug Products, HFD-570

THROUGH: Leslie Ball, M.D., Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Ele Ibarra-Pratt, RN, MPH
Consumer Safety Officer
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Domestic & Foreign Inspections

NDA: 21-746

SPONSOR: Discovery Laboratories, Inc.

DRUG: Surfaxin® (lucinactant)

CHEMICAL CLASSIFICATION: Type 1, S

THERAPEUTIC CLASSIFICATION: Synthetic Surfactant

INDICATIONS: Respiratory Distress Syndrome in Premature Infants

CONSULTATION REQUEST DATE: June 8, 2004

GOAL DATE TO PROVIDE INSPECTION SUMMARY: December 15, 2004

DIVISION GOAL DATE: January 14, 2005

PDUFA GOAL DATE: February 13, 2005

I. BACKGROUND:

Surfaxin® (lucinactant) is a synthetic lung surfactant for use in the prevention of respiratory distress syndrome (RDS) in premature infants. RDS occurs primarily in premature infants with greater risk in the very premature infant. Treatment may include supplemental oxygen, ventilator support, and surfactant replacement therapy. There

are currently four approved surfactants in the U.S.; three are naturally-based (Survanta, Infasurf, and Curosurf) and one synthetic-based surfactant (Exosurf). However, Exosurf is no longer marketed in the U.S.

The pivotal study (Protocol KL4-IRDS-06) in support of Surfaxin was conducted outside of the U.S. since the primary comparator arm, Exosurf, is not marketed in the U.S. The four sites (75, 30, 8, and 72) inspected were selected due to high enrollment. An inspection of the sponsor was also done since Surfaxin is a new molecular entity and in response to a request by the review division.

II. RESULTS (by site):

Name (site)	Country	Protocol	Insp. Date	EIR Recd.	Classn.
Janusz Gadzinowski, MD (75)	Poland	KL4-IRDS-06	11/8-11/12/2004	pending	pending
Vicente Salinas Ramirez, MD (30)	Mexico	KL4-IRDS-06	11/29-12/03/2004	pending	pending
Aldo Bernardo Santiago Bancalari Molina, MD (8)	Chile	KL4-IRDS-06	11/22-11/26/2004	pending	pending
Maria Kornacka, MD (72)	Poland	KL4-IRDS-06	11/15-11/19/2004	pending	pending
Discovery Laboratories	USA	KL4-IRDS-06	11/08-11/10/2004	pending	pending

Study Protocol: KL4-IRDS-06 “A Multinational, Multicenter, Randomized, Masked, Controlled, Prophylaxis Superiority Trial of the Safety and Effectiveness of Surfaxin (lucinactant) Compared to Exosurf (Colfosceril Palmitate) in the Prevention of Respiratory Distress Syndrome (RDS) in Premature Infants”

The objective of the pivotal study was to determine the difference in efficacy between Surfaxin and Exosurf and to assess the safety profile of Surfaxin compared to that of Exosurf and Survanta. The primary endpoint includes incidence of RDS at 24 hours of age and incidence of RDS-related mortality at 14 days of age, as determined by a 7 member Adjudication Committee. The Committee was provided with selected documents such as chest x-rays, case report forms, and autopsy data, when available. Standard operating procedures for the Committee were developed. The incidence of RDS at 24 hrs. was defined as positive changes by CXR at 24 hrs. (\pm 4 hrs.) and FiO₂ at 24 hrs. (\pm 4 hrs.) of $>$.30. Therefore, a neonate would be adjudicated as having no RDS if the FiO₂ at 24 hrs. was \leq .30 even though the CXR was found to be consistent with RDS. Premature infants up to 32 weeks gestation between 600-1250 grams were randomized to receive Surfaxin, Exosurf or Survanta at 15-30 minutes after delivery. Additional doses of surfactant were permitted if protocol-specified criteria were met indicating continued respiratory distress. Safety and efficacy were evaluated at 24 hours, 7 days, 14 days, 28 days, hospital discharge, 36 weeks post-conceptual age (after estimated date of confinement), and death. The four sites (75, 30, 8, and 72) inspected were selected due to high enrollment. An inspection of the sponsor was also done since Surfaxin is a new molecular entity and in response to a request by the review division.

Foreign Site Inspections

The medical officer selected the following four international sites for inspection due to high enrollment, and the fact that no domestic sites participated in the study.

Assessment Limitation: Please note that the following summary of the foreign inspections are based on the Form FDA 483 and discussions with the field investigator since the EIRs have not yet been received.

(1) **Janusz Gadzinowski, MD (site 75)**
Klinika Neonatologii
Akademii Medycznej w Poznaniu
Ul Polna 33
60-535 Poznan, Polska

FACTS#541205

This inspection assessed the investigator's conduct of the pivotal study: #KL4-IRDS-06. A total of 119 subjects were enrolled in the study. The following specific documents were audited: all of the informed consents, drug accountability records, chest x-rays, case report forms, IRB correspondence, and pertinent source documents. The inspector reviewed the following subject records:

751002	752020
751003	752028
751005	752031
751007	752037
751011	753002
751016	753008
751019	753022
751024	753025
751032	753030
752008	753043
752013	

The inspector verified the specific data points contained in the consult request from HFD-570 and as requested in the assignment that included a DSI Audit Form for the following subjects: 751002, 751024, 752008, 751005, 751007, 751016, 753008, 752020, and 752028. There were no discrepancies found.

The records and source documents for 21 of 119 subjects were reviewed in depth and compared to data sent with the assignment. All subjects met the entry requirements. There were no significant inconsistencies found between case report forms and source documents. All adverse events were listed in the case report forms. A Form FDA 483 was issued for a minor violation regarding the use of an informed consent dated 11/14/01 that was not IRB approved for subjects 751001, 751003, 752001, 752003, 752004, 753001, and 753002. However, the inspector reported that there were no significant differences between the IRB approved version and the version that was signed by these subjects. Data at this site appear acceptable.

(2) Vicente Salinas Ramirez, MD (site 30)

FACTS#541205

Instituto Nacional de Perinatologia
UCIN Primer Piso
Montes Urales #800
Lomas de Virreyes
Mexico, DF

This inspection assessed the investigator's conduct of the pivotal study: #KL4-IRDS-06. A total of 86 subjects were enrolled in the study. The following specific documents were audited: all of the informed consents, drug accountability records, chest x-rays, case report forms, IRB correspondence, and pertinent source documents. The inspector reviewed the following subject records:

301001	302017
301003	302028
301006	303012
301008	303014
301010	303016
301018	303020
302003	303042
302009	303049
302011 Died	(b) (6)

The inspector verified the specific data points contained in the consult request from HFD-570 and as requested in the assignment that included a DSI Audit Form for the following subjects: 303012, 303016, 303042, 303049, 301008,

301010, 302003, 303014, 301018, and 303020. There were no discrepancies found with exception to subject 303016; source documents could not be located to support information on ET obstruction.

The records and source documents for 17 of 86 subjects were reviewed in depth and compared to data sent with the assignment. A Form FDA 483 was issued on 12/3/2004 for the following observations:

1. **Subjects 301001, 301006 and 302009 did not meet inclusion/exclusion criteria.** Subject 301001 did not meet inclusion criteria due to a reported prolonged rupture of membranes of 6 days (> 5 days is exclusionary). Subject 301006 did not meet criteria because the site reported positive chorioamnionitis (clinical). Subject 301006 had reported adverse events that included neonatal sepsis (*staph epi.*) and seizures. Subject 302009 did not meet the protocol weight limitation (>1250 gm limit); patient weighed 1390 gm. Of note, subject 302009 did not appear in the EDR efficacy data listing. The site randomized subject 302009 to Survanta but was not dosed with the first dosing after the weight was found to be over the protocol limit. The subject was dosed with rescue surfactant (Exosurf), which is reportedly the standard treatment at this site. The subject was then dosed with the study surfactant for subsequent dosings.
2. **Subject 303016 source document information regarding ET obstruction was not found.** The source document to support the report of ET obstruction could not be found for this subject.
3. **Source documents (x-rays) were not available for Subjects 301006, 302005, 302009, 302016 303010, and 303013.** The inspection found that some of the original chest x-rays were discarded when the x-rays were in archives. However, the original x-rays were scanned onto the CD-ROMs during the study and the source documents support that the x-rays were performed.

The site was placed on temporary hold on three occasions in July 2002, June 2003, and August 2003 by the sponsor due to lack of adherence to ICH/GCP guidelines, protocol violations, data inconsistencies, and lack of adherence to the ventilator guidelines. In response to the holds, the site re-trained the staff and trained new residents on proper ventilator management.

The nature of the violations noted above at this site will probably warrant an untitled letter (VAI). Based on the small number of records audited and the multiple holds that were placed on this site, it appears that the site lacked attention to the details of the investigational plan.

(3) Aldo Bernardo Santiago Bancalari Molina, MD (08)

Hospital Clinico Regional
Guillermo Grant
Benavente
San Martin 1436
Concepcion, Chile

FACTS #541205

This inspection assessed the investigator's conduct of the pivotal study: #KL4-IRDS-06. A total of 65 subjects were enrolled in the study. The following specific documents were audited: all of the informed consents, drug accountability records, chest x-rays, case report forms, IRB correspondence, and pertinent source documents. The inspector reviewed the following subject records:

081001	081011
081014	082020 Died (b) (6) – Spleen Rupture
081015	082021
081017	083001
082004	083016 Died (b) (6) –Bronchopneumonia
082010	083024
082013	083025
082015	083026

The inspector verified the specific data points contained in the consult request from HFD-570 and as requested in the assignment that included a DSI Audit Form for the following subjects: 081017, 082004, 082010, 083026, 081011, 082015, 082020, 083024, 082013, and 083025. There were no discrepancies found.

The records and source documents for 16 of 65 subjects were reviewed in depth and compared to data sent with the assignment. All subjects met the entry requirements. There were no inconsistencies found between case report forms and source documents. All adverse events were listed in the case report forms. No Form FDA 483 was issued. Data at this site appear acceptable.

(4) Maria Kornacka, MD (72)

FACTS #541205

Oddzial Neonatologii
II Katedrji I Kliniki Ginekologii I Poloznictwa AM
Klinika Neonatologii ul Karowa
00-315 Warszawa, Poland

This inspection assessed the investigator's conduct of the pivotal study: #KL4-IRDS-06. A total of 63 subjects were enrolled in the study. The following specific documents were audited: all of the informed consents, drug accountability records, chest x-rays, case report forms, IRB correspondence, and pertinent source documents. The inspector reviewed the following subject records:

721001	722020
721004	722024
721007	723001
721012	723002
721013	723005
721015	723006
721016	723009
722001	723015
722005	723017
722010	723021
722012	723023
722014	
722015	

The inspector verified the specific data points contained in the consult request from HFD-570 and as requested in the assignment that included a DSI Audit Form for the following subjects: 721004, 722015, 723009, 723021, 721012, 721016, 722005, 722014, 721007, and 721013. There were no discrepancies found.

The records and source documents for 24 of 63 subjects were reviewed in depth and compared to data sent with the assignment. All subjects met the entry requirements. There were no inconsistencies found between case report forms and source documents. All adverse events were listed in the case report forms. No Form FDA 483 was issued. Data at this site appear acceptable.

III. Sponsor Inspection

Assessment Limitation: Please note that the following summary of the sponsor inspection is based on the draft EIR and discussions with the field investigator.

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

The purpose of the inspection was to obtain financial disclosure of the Adjudication Committee members and to review the Adjudication Committee ballots for selected subjects, which were included in the initial HFD-570 consult

request for the foreign inspections. In addition, DSI received an anonymous complaint against the sponsor for allegedly falsifying business records and data in support of Surfaxin. The financial disclosure statements were obtained from the sponsor prior to the inspection and forwarded to the medical officer.

The sponsor provided a copy of the Standard Operation Procedures Manual for the Adjudication Committee and completed voting ballots for selected subjects enrolled at sites 08, 30, 72 and 75 for auditing. The following is a list of the adjudication committee members, number of subjects adjudicated by members, and total number of meetings attended:

Adjudication Member	Specialty	Number of Subjects Adjudicated	Number of Meetings Attended
Soraya Abassi, MD	Neonatologist	467	31
Geoffrey Agrons, MD	Pediatric Radiologist	523	29
Sherry Courtney, MD	Neonatologist	443	20
Jacqueline Evans, MD	Neonatologist	681	31
Margaret Fernandes, MD	Neonatologist	216	26
Richard Markowitz, MD	Pediatric Radiologist	178	11
Kerry Weiss, MD	Neonatologist	528	25
Adjudication Committee	N/A	122	N/A

The following is a summary of the inspectional findings:

- In general, the sponsor adhered to their SOPs with a few exceptions. For example, the SOP required that conflicting votes for airleaks be referred to a pediatric radiologist if the initial votes were submitted by two neonatologists. For subjects 303020 and 751032, conflicting votes were submitted by neonatologists but these cases were referred to another neonatologist rather than a pediatric radiologist. Additionally, the SOP required that only two adjudicators initially review each case, however, there were three adjudicators documented for subject 751024.
- Dr. Evans adjudicated on more subjects than the other members. When the sponsor was asked to explain why Dr. Evans adjudicated on more subjects than the others, the sponsor stated that some members are more computer literate and are able to review the documents quicker than others (e.g., Dr. Evans). In addition, Dr. Evans attended the majority of the meetings that were scheduled monthly. Each member reportedly received an equal compensation for their services. Packages were sometimes sent to the members in advance of the meeting for review.
- There were some discrepancies noted with the airleak data received from HFD-570 data listings compared to the adjudicated airleaks from the voting ballots. The sponsor stated that airleak data was reported through two different sources: one source is derived from clinical investigator reports as recorded on the CRFs and the other source is derived from the results of the adjudicated airleaks. The sponsor stated that both sets of airleak data were reported in the NDA.
- The review of subject records did not reveal significant findings with the following exceptions: (1) For subject 303012, the sponsor was unable to find documentation that the FiO₂ was < .30 at 24 hours. The documents for subject 303012 show that the FiO₂ was “ND” and FiO₂ at 2 hrs. was 0.40 and at day 2 was documented between 0.40-0.90. (2) Subject 752028 was enrolled in the study with an exclusionary congenital anomaly, Trisomy 21.
- The inspection did not reveal find any information that substantiated the complaint based on our routine sponsor inspection and limited audit of patient records. Attempts at obtaining additional information from the complainant to better direct our inspection was unsuccessful; the complainant has not responded to additional inquiries.

The sponsor inspection did not reveal any issues of significance that warranted the issuance of a Form FDA 483.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, most of the sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol and signed informed consent. However, a number of deviations were noted at site 30, as noted herein.

No significant issues were identified during the sponsor inspection.

The data submitted in support of this NDA appear to be acceptable.

Follow-up action: None needed.

[**Note:** This Clinical Inspection Summary was based on the inspectional findings (FDA Form 483) and discussions with the field investigator since these inspections were recently conducted and the EIRs have not yet been received. Should the final review of EIRs and exhibits contain information that would significantly effect the classification or have an impact on the approval process, DSI will inform the Review Division in an amendment.]

Ele Ibarra-Pratt, R.N., M.P.H.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

DISTRIBUTION:

NDA 21-746
HFD-45/Division File
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/s/

Elinita Ibarra-Pratt
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CSO

Leslie Ball
1/5/05 06:26:27 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: December 15, 2004

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR of a **For Cause Directed** GLP Audit
Covering NDA 21-746, Surfaxin® (lucinactant)
Intratracheal Suspension, Sponsored by Discovery
Laboratories, Inc.

TO: Badrul A. Chowdhury, M.D.
Director
Division of Pulmonary Drug Products (HFD-570)

At the request of HFD-570, the Division of Scientific Investigations conducted an audit of the following non-clinical study:

Study Number: (b)(4) 02-003
Study Title: Fourteen-day intratracheal instillation of lucinactant in rabbits with a 28-day recovery.

Study (b)(4) 02-003 was conducted at (b)(4)

Background: This inspection was requested by HFD-570 primarily to confirm that the rabbits in new born Study (b)(4) 02-003 were **three weeks old**. The request stemmed from discrepancies between the new born studies proposed by the sponsor versus the study submitted in the NDA. The sponsor initially proposed a 14-day newborn study using 5-week old rabbits, which the Agency found unacceptable as 5-week old rabbits are not new born animals. Later, the sponsor proposed to use 14-day old cats, which was acceptable to the Agency. However, the sponsor did not submit the proposed cat study, instead submitted Study (b)(4) 02-003 using 3-week old rabbits.

Non Clinical Study Site: [REDACTED] (b)(4)

DSI expedited this inspection following notification by [REDACTED] (b)(4) that the facility will be closing operations. The inspection at [REDACTED] (b)(4) found that the facility was not operational. No Form 483 was issued following the inspection. However, the inspection revealed the following:

- The documents and specimen for Study [REDACTED] (b)(4) 02-003 and other studies involving Surfaxin were transferred to the sponsor. The Agency was not notified of the transfer.
- The 20-month delay between study conduct and report finalization was due to departure of the original study director, six months following study conduct. The new study director took additional time to complete the final report, as final reports for many studies had to be completed.
- The master schedule revealed that [REDACTED] (b)(4) also conducted a new born study, [REDACTED] (b)(4) 03-101, in 14-day old cats involving Surfaxin. In addition, a second cat study was planned but was never initiated.

Sponsor Site: Discovery Laboratories, Doylestown, PA

A follow-up inspection (12/6-9/04) was conducted at Discovery Laboratories, Doylestown, PA for data audit of study [REDACTED] (b)(4) 02-003. The raw data for the study was available at the site and was audited. The tissue blocks and specimen were not available, as they were transferred by the sponsor to a contract archives.

The data audit confirmed that the rabbits used in Study [REDACTED] (b)(4) 02-003 were three weeks old at the initiation of dosing. The audit did not reveal discrepancies between the final report and the raw data. Also, the sponsor stated that the new born study in 14-day old cats, [REDACTED] (b)(4) 03-101, was submitted as part of the NDA. HFD-570's pharmacology/toxicology review of the NDA confirmed that Study [REDACTED] (b)(4) 03-101 was submitted.

Following the inspection, Form 483 was issued. The objectionable findings listed related to the failure of sponsor's archives to store records as per GLP regulations. Although the objectionable practices should be corrected, they do not impact the acceptability of study data.

Conclusion:

The animals in study (b) (4) 02-003 were confirmed to be 3 weeks old. DSI recommends that the study data be accepted for Agency review.

After you have reviewed this memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Final Classifications:

NAI - (b) (4)
VAI - Discovery Laboratories Inc., Doylestown, PA

cc:

HFA-224

HFD-45/RF

HFD-48/Subramaniam/Himaya/CF

HFD-570/Yu

HFD-570/Hao/Sun

HFR-CE150/Laska

Draft: SS 12/13/04

Edit: MFS

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/s/

Amalia Himaya

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CSO

Dr. O' Shaughnessy (Acting for Dr. Viswanathan) signed the
paper copy on 12/17/04. Paper copy available upon
request.



Memorandum

Pre-Decisional Agency Information

Date: October 18, 2004

To: Christine Yu, R.Ph.
Regulatory Project Manager
DPADP, HFD-570

From: Jialynn Wang, Pharm.D.
Iris Masucci, Pharm.D.
DDMAC, HFD-42

Subject: NDA 21-746
DDMAC comments on Surfaxin (lucinaquant) Intratracheal
Suspension draft PI

DDMAC has reviewed the draft PI for Surfaxin and has the following comments:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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/s/

Jialynn Wang
10/18/04 10:50:23 AM
DDMAC REVIEWER

DSI CONSULT

Request for GLP Inspections

DATE: October 5, 2004

TO: C.T. Viswanathan, Ph.D.
Chief, Good Laboratory Practice/Bioequivalence Branch
Division of Scientific Investigations, HFD-48

THROUGH: Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary & Allergy Drug Products, HFD-570

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

SUBJECT: Request for GLP Inspection
NDA 21-746
Surfaxin (lucinactant) Intratracheal Suspension

Study/Site Identification:

The following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Lab Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
02-003	White Eagle Toxicology Laboratories 2003 Lower State Road Doylestown, PA 18901 Study Director- George L. Brown QA Manager- Nicholas J Meo No phone number provided	

Goal Date for Completion:

Background information for the requested GLP inspection is provided with the consult. We request that the inspections be conducted and the Inspection Summary Results be provided by **December 15, 2004**. We intend to issue an action letter on this application by **January 7, 2005**.

Should you require any additional information, please contact Christine Yu @ 301-827-1051.

Application: NDA 21-746, original submission
Date: April 13, 2004
Product: Surfaxin (lucinactant) Intratracheal Suspension
Sponsor: Discovery laboratories, Inc.
Intended Clinical Population: Premature infants with respiratory distress syndrome
Review Division: Division of Pulmonary and Allergy Drug Products, HFD-570
Pharmacologist: Huiqing Hao, Ph.D.
Supervisory Pharmacologist: Joseph Sun, Ph.D.

Study to be audited:

Title: Fourteen-day intratracheal instillation of lucinactant in rabbits with a 28-day recovery
Conducting lab: White Eagle Toxicology Laboratories
2003 Lower State Road
Doylestown, PA 18901
Study number: White eagle study number: 02-003
Study Initiation Date: October 18, 2000
GLP: The study report is accompanied with a GLP statement
QA: Yes

Reason for audit request:

This study was initiated on 10/18/2000.
Protocol in place on 01/07/2002.
Started on 03/07/2002.
Completed on 04/25/2002
Reported to Study Director and Management 6 times during the period of 05/16/2002 to 10/01/2002/
Signed off on 12/22/2003 by Study Director and Manager of Quality Assurance.

During the pre-NDA meeting on 06/13/2003 (meeting minutes faxed 07/12/2003), Discovery inquired whether the preclinical program was sufficient to support the Surfaxin NDA for RDS, once the newborn toxicity studies in two non-rodent species were complete.

Division concurred that new born studies with 14 day dosing in 2 different species can be used to support the NDA.

Since one 14-day study had been conducted in pups, Discovery asked if a 14-day toxicity study using 5-weeks old rabbits would be acceptable as one of two 14-day newborn studies. The Division determined that using 5-weeks old rabbits were not acceptable since they were of weaning age.

On 08/12/2003, Discovery submitted a proposal to use 3-4 weeks old cats for this study. Division did not find this proposal acceptable. On 09/25/2003, Discovery submitted a proposal to use 14-day old cats

for the newborn study, and the Division concurred on 10/14/2003. Accordingly, the Division expected a study in 14-day old cats to be submitted in the NDA.

The NDA, however, contains a study using 3-weeks old rabbits. In light of the past animal age issue, a study completion date of 04/25/2002, and a sign off date of 12/22/2003, it is unclear whether the rabbits used in the study were 3 weeks old at the initiation of dosing. Therefore, we are requesting a GLP investigation for this study.

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/s/

Christine Yu
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Paper copy of consult to be sent by mail.
Volume 1.1 of Module 1 (CTD NDA) included
with consult.

DSI CONSULT: Request for Clinical Inspections

Date: June 8, 2004

To: Ele Ibarra-Pratt, R.N., MPH., CSO/HFD-47

Through: Joanne L. Rhoads, M.D., Director, DSI, HFD-45
Badrul Chowdhury, M.D., Ph.D., Director, HFD-570

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

Subject: **Request for Clinical Inspections**
NDA 21-746
Discovery Laboratories, Inc.
Surfaxin (lucinactant) Intratracheal suspension

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Prevention of RDS in premature neonates	KL4-IRDS-06	1) Janusz Gadzinowski, MD Klinika Neonatologii Akademii Medycznej w Poznaniu Ul Polna 33 60-535 Poznan, Polska	1) 119
		2) Vicente Salinas Ramirez, MD Instituto Nacional de Perinatologia UCIN Primer Piso Montes Urales #800 Lomas de Virreyes Mexico, DF	2) 86
		3) Aldo Bernardo Santiago Bancalari Molina, MD Hospital Clinico Regional Guillermo Grant Benavente San Martin 1436 Concepcion, Chile	3) 65
		4) Maria Kornacka, MD Oddzial Neonatologii II Katedrji I Kliniki Ginekologii I Poloznictwa AM Klinika Neonatologii ul Karowa 00-315 Warszawa, Poland	4) 63

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

International Inspections:

We have requested inspections because (please check appropriate statements):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: pivotal study was conducted outside of U.S.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **December 15, 2004**. We intend to wrap up this application by (action goal date) **January 7, 2005**.

Should you require any additional information, please contact Christine Yu @ 301-827-1051 or by e-mail yuc@cdcr.fda.gov.

cc: Peter Starke, M.D., Medical Team Leader
J Harry Gunkel, M.D., Medical Reviewer
Leslie Ball, M.D., GCP II, Branch Chief

**DSI Audit
NDA 21-746
Surfaxin® (lucinactant) Intratracheal Suspension
Discovery Laboratories, Inc.**

Background

This NDA is for the synthetic lung surfactant, Surfaxin, for the “prevention of RDS in premature infants.” There is one pivotal study: KL4-IRDS-06, “A Multinational, Multicenter, Randomized, Masked, Controlled, Prophylaxis Superiority Trial of the Safety and Effectiveness of Surfaxin® (lucinactant) Compared to Exosurf® (colfosceril palmitate) in the Prevention of Respiratory Distress Syndrome (RDS) in Neonates” (*study report: module 5, section 5.3.5.1, p 1*). In addition to the superiority comparator product, Exosurf, a reference product, Survanta®, was also used in the study. KL4-IRDS-06 was conducted in 54 centers in Europe and Latin American. One center was in the U.S., but no patients were enrolled there.

There are three endpoints of interest for this audit:

1. Death. RDS can be a fatal disease in premature neonates if not treated, so death was an efficacy endpoint for this study. The audit should verify whether a patient died and the date of death if it occurred.
2. Air leak. Air leak may be a frequent occurrence in neonates with RDS and was a secondary endpoint in this study, as well as serving as a safety endpoint. There are several different types of air leak: pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema, and subcutaneous emphysema. The audit should verify whether or not air leak(s) occurred, the type(s), and date(s). The air leak would be documented in the medical or nursing notes and/or in radiology reports.
3. Endotracheal tube (ET) obstruction. All surfactant products are administered as liquids that are instilled into the neonate’s endotracheal tube. A possible complication that may have clinical consequences is obstruction of the tube by the surfactant before it disperses into the lungs. It is important to know whether there are any differences in the frequency of obstruction between the different types of surfactant. The audit should verify whether or not obstruction occurred.

Sites for Audit

Four of the 54 study sites are proposed for audit. They were selected because they are the four highest enrolling centers in the study. Review of other factors (number of deaths, number of protocol violations, number of SAE’s, etc.) at all centers failed to reveal any more compelling bases for site selection. The sites, PI’s, and number of patients are shown in Table 1.

Table 1: KL4-IRDS-06 Study Sites for DSI Audit

Study Center Number	Principal Investigator/Address	N
75	Janusz Gadzinowski, MD Klinika Neonatologii Akademii Medycznej w Poznaniu Ul Polna 33 60-535 Poznan, Polska	119
30	Vicente Salinas Ramirez, MD Instituto Nacional de Perinatologia UCIN Primer Piso Montes Urales #800 Lomas de Virreyes Mexico, DF	86
8	Aldo Bernardo Santiago Bancalari Molina, MD Hospital Clinico Regional Guillermo Grant Benavente San Martin 1436 Concepcion, Chile	65
72	Maria Kornacka, MD Oddzial Neonatologii II Katedrji I Kliniki Ginekologii I Poloznictwa AM Klinika Neonatologii ul Karowa 00-315 Warszawa, Poland	63
<i>Module 5, Section 5.3.5.1, p. 633; Module 5, Section 5.3.5.1, p. 1786</i>		

Following are tabulated lists of study patients selected for audit at each of the sites. Ten patients from all treatment groups were selected at each site. The result for each patient for each endpoint discussed above is listed with space for the finding of the auditor to be added.

Table 2: Dr. Gadzinowski; Poznan, Poland

Patient Number & Treatment	Death		Air Leak		ET Obstruction	
	NDA	DSI	NDA	DSI	NDA	DSI
751002 – Surfaxin	(b) (6)		Yes PTX 2/19/02 PIE 2/22/02		Yes 2/19/02	
751024 – Surfaxin			No		No	
751032 – Surfaxin			No		No	
752008 – Surfaxin			Yes PIE 5/1/02		No	
751005 – Exosurf			Yes PIE 9/12/02		Yes 9/10/02	
751007 – Exosurf			Yes PIE 9/24/02		No	
751016 – Exosurf			Yes PIE 2/28/03		No	
753008 – Exosurf			Yes PTX 5/18/02		No	
752020 – Survanta			Yes PIE 11/19/02		Yes 11/20/02	
752028 –			No		No	

Patient Number & Treatment	Death		Air Leak		ET Obstruction	
	NDA	DSI	NDA	DSI	NDA	DSI
Survanta						
	<i>Module 5, Sec 5.3.5.1, p 10374</i>		<i>Module 5, Sec 5.3.5.1, p 10374</i>		<i>Module 5, Sec 5.3.5.1, p. 5585</i>	

Table 3: Dr. Salinas Ramirez; Mexico, D.F.

Patient Number & Treatment	Death		Air Leak		ET Obstruction	
	NDA	DSI	NDA	DSI	NDA	DSI
303012 – Surfaxin	No		No		Yes 6/05/02	
303016 – Surfaxin	(b) (6)		No		Yes 7/02/02	
303042 – Surfaxin			Yes PIE 3/11/03		No	
303049 – Surfaxin			No		No	
301008 – Exosurf			Yes 8/05/02		Yes 8/03/02	
301010 – Exosurf			No		No	
302003 – Exosurf			No		No	
303014 – Exosurf			No		Yes 6/19/02	
301018 - Survanta			No		No	
303020 – Survanta			Yes PIE 9/17/02		No	
		<i>Module 5, Sec 5.3.5.1, p 10374</i>		<i>Module 5, Sec 5.3.5.1, p 10374</i>		<i>Module 5, Sec 5.3.5.1, p. 5585</i>

Table 4: Dr. Molina; Concepcion, Chile

Patient Number & Treatment	Death		Air Leak		ET Obstruction	
	NDA	DSI	NDA	DSI	NDA	DSI
081017 – Surfaxin	(b) (6)		No		No	
082004 - Surfaxin			No		No	
082010 – Surfaxin			No		No	
083026 - Surfaxin			No		No	
081011 – Exosurf			Yes PIE 7/24/03		No	
082015 – Exosurf						
082020 – Exosurf				No		No
083024 – Exosurf			Yes PTX 7/24/03		No	
082013 – Survanta			No		No	
083025 –		No		No		No

Patient Number & Treatment	Death		Air Leak		ET Obstruction	
	NDA	DSI	NDA	DSI	NDA	DSI
Survanta						
	<i>Module 5, Sec 5.3.5.1, p 10374</i>		<i>Module 5, Sec 5.3.5.1, p 10374</i>		<i>Module 5, Sec 5.3.5.1, p. 5585</i>	

Table 5: Dr. Kornacka; Warsaw, Poland

Patient Number & Treatment	Death		Air Leak		ET Obstruction	
	NDA	DSI	NDA	DSI	NDA	DSI
721004 – Surfaxin	No		No		Yes 4/12/02	
722015 – Surfaxin	No		Yes 3/13/03		Yes 3/11/03	
723009 – Surfaxin	No		No		No	
723021 – Surfaxin	No		No		No	
721012 – Exosurf	(b) (6)		Yes PIE 7/23/03 PTX 7/24/03		No	
721016 – Exosurf	(b) (6)		Yes PIE 8/13/003		Yes 8/13/03	
722005 – Exosurf	(b) (6)		Yes PIE 5/31/02		No	
722014 – Exosurf	(b) (6)		Yes PTX 2/23/03		No	
721007 – Survanta	(b) (6)		No		Yes 5/30/02	
721013 – Survanta	(b) (6)		Yes PTX 5/27/03		Yes 5/27/03	
	<i>Module 5, Sec 5.3.5.1, p 10374</i>		<i>Module 5, Sec 5.3.5.1, p 10374</i>		<i>Module 5, Sec 5.3.5.1, p. 5585</i>	

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/s/

Badrul Chowdhury
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