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APPLICATION NUMBER:

021746Orig1s000

OTHER ACTION LETTERS



NDA 21-746

COMPLETE RESPONSE

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

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

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

We acknowledge receipt of your amendments dated October 17, 2008, and February 12 and March 12, 2009. The October 17, 2008, amendment constituted a complete response to our May 1, 2008, action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. You have not adequately addressed Comment 14 of our May 1, 2008, letter and the associated comment in the discussion section of Question 1a of the minutes of the June 18, 2008, telephone conference. Comment 14 requests that you tighten the acceptance criteria for the drug product biological activity and validate the fetal rabbit biological activity assay. Question 1a requests that you repeat a lamb study as a link for validating the fetal rabbit assay. Your resubmission, however, has not adequately satisfied these requests because the results of lucinactant activity in the lamb and rabbit studies were inconsistent. The rabbit assay failed to distinguish effects of expiry status on lucinactant efficacy while the lamb study did. In addition, the fetal rabbit assay has not been adequately validated.

To address the above deficiencies, conduct one of the following options:

- a. Validate the fetal rabbit assay by linking it to the results of fetal lamb studies. Demonstrate the ability of the rabbit bioassay to differentiate lucinactant activity between the expired and unexpired batches or lots as was observed with the lamb model.

- b. Develop and demonstrate that the lamb model is a reliable bioassay for testing lucinactant activity. This assay should then be used to assess the potency as part of regulatory specifications of drug product lots.
 - c. Conduct necessary clinical trials and nonclinical studies to validate any other bioassay to assess lucinactant potency and specifications prior to release.
2. Comment 11c, from our May 1, 2008, letter remains a deficiency. The qualification data for the study in ferrets do not support the proposed acceptance criterium for the (b) (4) - related) impurity in the drug product. Tighten the acceptance criterium to not more than (b) (4) or provide adequate safety data to qualify this impurity.

LABELING

New labeling requirements and the implementation plan for complying with those requirements were published in the *Federal Register* on January 24, 2006 (“Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products,” 71 *FR* 3922). All applications submitted on or before June 30, 2006, must comply with these requirements at the time of approval if the application is approved after June 30, 2009. Therefore, any resubmission of this application must include physician labeling in the format found at current 21 CFR 201.56 and 57. Additional information about these labeling requirements can be found at <http://www.fda.gov/cder/regulatory/physLabel/default.htm>.

We reserve further comment on the proposed labeling until the application is otherwise adequate. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

PROPRIETARY NAME REVIEW

We have completed our review of the proposed proprietary name, Surfaxin, and have concluded that it is acceptable. Surfaxin will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for re-review.

RELIANCE ON LITERATURE

Applications that rely to any extent on published literature are considered to be 505(b)(2) applications if the applicant has not obtained a right of reference to the raw data underlying the published study or studies. If your resubmission of this application depends upon a published study (e.g., *Pediatrics*, 117:295-303), that is, if the published study is essential to approval of the application, it will be considered to have been submitted pursuant to section 505(b)(2) of the FDCA unless you have a right of reference to, or own, the underlying data. For more information, see our draft Guidance for Industry titled *Applications Covered by Section 505(b)(2)* which can be found at <http://www.fda.gov/cder/guidance/2853dft.pdf>. If you have a right of reference or ownership of the underlying data, it should be documented in your resubmission.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

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

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

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebaugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Curtis Rosebraugh
4/17/2009 10:57:51 AM



NDA 21-746

NDA APPROVABLE

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

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

Dear Dr. Hurley:

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

We acknowledge receipt of your submissions dated October 31, November 12, and December 21, 2007, and January 4 and 18, February 29, and April 10, 21, and 29, 2008.

The October 31, 2007, submission constituted a complete response to our March 31, 2006, action letter.

We have completed our review of this application, as amended, and it is approvable. However, before the application may be approved, it will be necessary for you to acceptably address the following comments:

1. Provide a data summary to support the efficacy of the (b) (4) process through (b) (4) (b) (4) and demonstrate compatibility of the (b) (4) with the drug product.
 - a. Include (b) (4) test results from three (b) (4) lots used in the (b) (4) studies.
 - b. Provide a narrative of the method used in the (b) (4) validation study and list the approved SOP.
2. With regard to the validation of process hold time between the formulation bulk and the final filling step, provide a bioburden data summary to justify this hold time.
3. Provide a data summary of the most recent successful (b) (4) qualification demonstrating removal of particles or endotoxin from the washed vials. Include a narrative of the method used in the (b) (4) qualification study and list the approved SOP.

4. With regard to the (b) (4), provide a data summary from three consecutive successful validation runs with acceptable (b) (4) results.
 - a. Identify the location of (b) (4) vials.
 - b. Include the time spent by the vials in the (b) (4).
 - c. Provide a narrative of the method used in the (b) (4) qualification study and list the approved SOP.
5. Identify the (b) (4) that will be used to (b) (4) equipment. Provide the following information for that (b) (4) if multiple units are used in the production.
 - a. Identify the production cycle and the validation cycle parameters.
 - b. Provide a data summary from three consecutive successful validation runs with acceptable (b) (4) results.
 - c. Identify the minimum and maximum (b) (4) used in the validation.
 - d. Provide summary results from the latest re-qualification, if performed.
 - e. Provided a narrative of the method used in the qualification study and list the approved SOP.
6. For the (b) (4) provide a data summary from three consecutive successful validation runs with acceptable (b) (4) results.
 - a. Identify the equipment pieces that will be (b) (4) processed together or separately.
 - b. Identify the (b) (4) and the location of each Biological Indicator.
 - c. Provided a narrative of the method used in the (b) (4) qualification study and list the approved SOP.
7. Provide a data summary from the three most recent media fills conducted to qualify the filling line you propose to use in the manufacture of Surfaxin.
 - a. State the acceptance criteria for the media fill simulation in keeping with the Agency's (b) (4) guidance.
 - b. Identify the filling line for which this process simulation was conducted.

- c. Identify the dates on which the three consecutive media fills were conducted.
 - d. Identify the vial stopper combination used during media fill simulation.
 - e. State the number of vials rejected prior to incubation.
 - f. State the number of vials actually incubated.
 - g. State the number of vials showing growth after incubation for 14 days.
 - h. Provided a narrative of the process validation through Media Fill simulation study and list the approved SOP.
8. Provide results from the environmental monitoring that was performed concurrently with the most recent media fill process simulation for the release of the filling line for Surfaxin.
9. Provide the following information pertaining to Microbial Ingress and the Dye Immersion tests that were performed to demonstrate integrity of the container/closure system:
- a. Microbial Ingress Test.
 - 1) State the acceptance criteria for the test to be successful.
 - 2) State the number of sealed vials used in the study.
 - 3) State the concentration of *B. diminuta* used to make the test suspension.
 - 4) Provide a narrative of the validated Microbial Ingress Test method and list the approved SOP.
 - b. Dye Ingress Test.
 - 1) State the acceptance criteria for the test to be successful.
 - 2) State the number of sealed vials used in the study.
 - 3) State the concentration of Methylene Blue used to make the test suspension.
 - 4) State the amount of vacuum applied to the immersed vials.
 - 5) Provide a narrative of the validated Methylene Blue Test method and list the approved SOP.

10. Provide a method validation summary for the Bacterial Endotoxins test used to qualify the process validation batches and the stability batches. Include the established MVD for Surfaxin based on your reagent sensitivity.
11. Submit revised drug substance specifications to include the following.
 - a. Tighten the proposed acceptance criteria for (b) (4), to coincide with the submitted data and manufacturing capabilities.
 - b. The drug substance impurities related to (b) (4) exceed the ICH-recommended thresholds for identification and qualification, and they were not included in the ferret study. Limit the proposed acceptance criteria for individual impurities, with the exception of (b) (4) impurity, to not more than (b) (4) or provide adequate safety data to qualify these impurities. Refer to comment 1 in our March 31, 2006, letter.
12. Clarify your response to comment 7 in our March 31, 2006, letter. Specify for which drug product batches the overage of (b) (4) was used, and which batches were manufactured to a (b) (4) sinapultide concentration. Submit a revised drug product composition table as well as other parts of the NDA that are affected by the concentration change of sinapultide.
13. Submit revised drug product specifications to include the following.
 - a. Revise the acceptance criteria for the content of each active ingredient to include the target values in the specification table.
 - b. Tighten the proposed acceptance criteria for the (b) (4) impurities. We note that the (b) (4) and reduce the biological activity of the drug product. Refer to table 20-1, which was provided in response to comment 20 in our March 31, 2006, letter.
 - c. The provided qualification data for the study in ferrets do not support the proposed acceptance criteria for the (b) (4) impurity in the drug product. Tighten the acceptance criteria to not more than (b) (4) or provide adequate safety data to qualify this impurity.
 - d. Justify the proposed (b) (4) of the vial and submit supporting data or reduce the proposed overfill. Revise the acceptance criteria for the volume in container to include target values and acceptable ranges for the fill volume, and for the nominal fill volume.

14. Comment 10 in our March 31, 2006, letter remains as a deficiency. Tighten the proposed acceptance criteria for the drug product biological activity and respond to the following comments regarding the analytical method DP-018 and the method validation.

a. Analytical test method DP-018 (lucinactant bioassay in rabbits):

- 1) Justify the use of the lucinactant dose in this assay. The dose to be used for lucinactant (8 mL/kg) is higher than the proposed clinical dose (5.8 mL/kg), the dose used in the neonatal lamb study conducted previously (5.8 mL/kg), and the dose to be tested for positive control (Survanta, 5.6 mL/kg).
- 2) Justify the criterion for a positive result for lucinactant bioactivity. In the protocol, the criterion was defined as Crs at 30 minutes \geq 2-fold of the air control value. This definition differs from our recommended criterion of \geq 3-fold.
- 3) Provide acceptance criteria for positive controls.
- 4) In the section "qualification of positive controls," you stated "The ratio of the mean positive control Crs to mean negative control Crs will be calculated and expressed as a percentage for 10 assays. The average and standard deviation (SD) of the natural log-transformation of these 10 values will be calculated. The threshold for mean Crs ratio of positive control versus negative control in a test will be determined by the exponential of the difference between the average and the product of 2.58 times the standard deviation rounded to closest 50%." Explain this statement in order to clarify the expression of the data and the rationale for not using the same expression as that to be used for lucinactant activity.

b. Validation study for the method DP-018:

This study provided inadequate data to validate the rabbit bioactivity assay. Reconduct the study to include the following:

- 1) As stated in the methodology for DP-018, include a positive control (e.g., Survanta) in the study.
- 2) Test at least three lots of lucinactant as discussed in the meeting on December 21, 2006.
- 3) Provide a complete study report including a clear description of the study method (test article identification, lot numbers, purity, dates of expiration, doses, group sizes, unit of measurements) and results (description and summary tables of the study results including mean value and standard deviation of the measurements, and line listing of individual animal data).

15. As requested in our December 11, 2007, communication, provide a detailed overview of manufacturing changes implemented at the Totowa, NJ, drug product manufacturing site, with specified completion dates for all changes. Explain what changes were implemented after the manufacture of stability batches T7002, T7003, and T7004. Provide an update to the pending stability data with statistical evaluation.
16. As requested in comment 18 of our March 31, 2006, letter, retain stability testing for both storage orientations until the recent process/container closure changes are properly validated and an adequate amount of data is accumulated. Provide revised stability protocol STABPROT-51 and a comparison of the stability data for both storage orientations collected on drug product batches that are representative of the commercial product.
17. Submit a revised Methods Validation package upon implementation of the requested changes. Refer to comment 14 in our March 31, 2006, letter.
18. Comment 6 in our February 11, 2005, letter and comment 5 in our March 31, 2007, letter remain deficient. We note that this application was resubmitted for review on October 31, 2007, with the statement that “all manufacturing and testing sites are ready for inspection,” even though the deficiencies remained from the last GMP inspection (Form FDA 483, dated September 24, 2007) and the site remained unavailable for inspection (i.e., closed for manufacturing and equipment changes) for most of the current review cycle. Satisfactory inspections of all sites are required before this application may be approved.

Submit an updated list of all manufacturing and testing sites supporting your application. Include a detailed description of the manufacturing and/or testing responsibilities of each site and include a statement that the site is ready for inspection.

In addition, it will be necessary for you to submit draft labeling as follows:

1. Content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the draft labeling for the package insert submitted on April 29, 2008.
2. Revised mock-up labels for all vial and carton presentations for the to-be-marketed drug product, incorporating the following preliminary comments.
 - a. Provide composition information.
 - b. Specify dosage per kilogram of body weight.
 - c. Next to the drug product name, include drug product volume per container.
 - d. Emphasize the statements “Not for Injection” and “Single Use Vial”.

- e. Increase the prominence of the nonproprietary name “(lucinactant) Intratracheal Suspension”.
- f. Remove the promotional statement (b) (4)

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

We continue to encourage you to consider additional dose-ranging clinical studies with Surfaxin. The additional information could help to determine whether negative reactions to dose administration could be reduced without affecting efficacy.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Pulmonary and Allergy Products to discuss what steps need to be taken before the application may be approved.

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

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

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Curtis Rosebraugh
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NDA 21-746

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

Attention: Christopher J. Schaber, Ph.D.
Executive Vice President, Drug Development and Regulatory Compliance

Dear Dr. Schaber:

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

We acknowledge receipt of your submissions dated April 8, July 13 and 29, October 5, November 2, and December 9, 2005, and January 4 and March 2, 2006.

The October 5, 2005, submission constituted a complete response to our February 11, 2005, action letter.

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

1. Item 1 in our letter dated February 11, 2005, remains a deficiency. Submit revised specifications sheets for all active pharmaceutical ingredients (API) as requested in Item 1, and in the additional comments provided in our correspondence dated August 16, 2005.
 - a. Include full impurity profiles. Note that each individual impurity has to be listed by name, and not as "individual" or "related." Those individual impurities that have not been identified yet, but which occur regularly, should be characterized by corresponding relative retention times (RRT), similar to data listed in tables 2-1 through 2-4 on pages 20-27 of the October 5, 2005, submission. For example, Table 2-4 on page 26, lists about 17 individual impurities (b)(4) with 6 of them identified by name and the remaining 11 impurities characterized by the RRT. However, the proposed specifications list only "individual NMT (b)(4) and "total NMT (b)(4) impurities. Refer to ICH Q3A Guidance and to our comments below on the qualification of impurities (Item 2). Attach a sheet listing each identified impurity, with proper chemical name and structure, to each specification sheet.

- b. Submit side-by-side confirmatory data from testing performed by you and by each API manufacturer, and clearly specify the methods and testing laboratory for each attribute. Although sending samples “in a blinded fashion” back to the manufacturer may prove useful during the method development and transfer, it is not an acceptable solution for routine verification of the incoming drug substance. Clarify how many batches of each API you are receiving per year from the corresponding manufacturer.
 - c. Provide justification for the proposed acceptance criteria for each impurity profile, based on the analysis of the test results obtained when using a current and validated analytical method. Include at least two significant numbers after the decimal for the proposed acceptance criteria, e.g., 1.00 % instead of 1 %.
 - d. Currently you utilize only one type of analytical procedure for the confirmatory testing of the identity and structure of the sinapultide peptide, i.e., reverse-phase HPLC methods for identity, assay, impurities, and (b) (4) (DS-001, DS-004 and DS-005). At a minimum, include the test for amino acid analysis to assure control of the primary structure of the peptide, and mass spectrometry testing for additional identity testing.
 - e. We note changes in the drug substance attributes/profiles for the (b) (4) proposed in the submission dated October 5, 2005, as compared to the original application. For example, Table 2-1 on page 21 lists (b) (4) whereas the original application listed acceptance criteria for (b) (4) and in the revised acceptance criteria (see submission dated October 5, 2005) only (b) (4) and “others” are listed. Include all (b) (4) in each of the drug substance specifications and clarify whether any changes have taken place in the drug substance manufacturing/purification processes since the original application.
2. Provide adequate safety qualifications to support the proposed specifications for all identified drug substance and drug product impurities or reduce the specifications to those recommended in ICH Guidances Q3A(R) and Q3B(R). The submitted 7-day impurity qualification study in rabbits and the rationale based upon previously conducted toxicology studies do not provide adequate information to qualify the proposed impurity specifications. Specifically, the impurities were either administered to animals at daily doses that were lower than the maximum expected daily human dose or were not identified in the administered batches. Specifications above the ICH recommended levels should be associated with daily human doses that have been demonstrated to produce no significant toxicity, usually in animal studies, with the inclusion of adequate safety margins.
3. Item 3 in our letter dated February 11, 2005, remains a deficiency. We are awaiting responses from the holders of drug master files (DMFs) (b) (4). Any complete response to this letter must include a statement that the DMFs listed above have been amended with a complete response to all deficiencies and requests. Also, list the dates each DMF was amended to correct the conveyed deficiencies, similar to the table provided on page 28 of your October 5, 2005, submission.

4. Item 4 in our letter dated February 11, 2005, remains a deficiency. Although the list of the presented supportive data seems adequate, the submitted stability data lack important attributes (e.g., impurity profiles, biological activity – not measured or reported as “pass”) to allow the assessment of the comparability of the drug product used in pivotal clinical trials to the to-be-marketed drug product. Submit a side-by-side comparison of the stability results grouped by the attribute, storage orientation, and storage conditions, for the “pre-change” and “post-change” batches. Provide an update to the stability results collected on the “post-change” batches.
5. Item 6 in our letter dated February 11, 2005, remains a deficiency. This application cannot be approved until all supporting manufacturing and testing sites have an acceptable recommendation from our Office of Compliance. As a part of your complete response, provide a statement informing us that the drug product manufacturing site is ready for re-inspection and all deficiencies have been adequately addressed. Submit a table listing all GMP deficiencies and corresponding dates for the final corrective actions.
6. Item 7 in our letter dated February 11, 2005, remains a deficiency.
 - a. Provide data summaries for three consecutive process validation experiments (media fills) using the new container/closure system and the quality systems in place under the new ownership. Identify changes/improvements in your (b) (4) process with a brief summary and/or with change control documentation. Identify the personnel responsible for (b) (4) processing and the Quality Control of the (b) (4) production process.
 - b. Provide a data summary of container/closure integrity testing for the new package configuration and include container/closure integrity testing in your stability protocol at start and at expiry time points.
 - c. Describe the steps taken to assure prevention of potential product contamination during the raw materials acquisition, storage, weighing, and transportation to the manufacturing plant. Include Standard Operating Procedures (SOPs) or summaries of SOPs.
 - d. Describe the steps taken to assure that the drug product does not become contaminated subsequent to the (b) (4) and prior to (b) (4). Include SOPs or procedures put in place for (b) (4) handling and monitoring as appropriate.
 - e. DMF (b) (4), supporting the drug product manufacture, is inadequate. We note your statement informing us about your plans to submit a DMF update in March 2006. Information and data that are not product specific may be submitted in a DMF provided that the submission date(s) and page numbers are identified in the letter of authorization and cross-referenced to the NDA.
7. Regarding your response to Item 8 from our letter dated February 11, 2005, provide a report on further investigation of (b) (4) steps. Describe interactions and changes to APIs occurring during drug product manufacture and employ it as a tool to decreasing/eliminating drug substance overages.

8. Regarding the drug product batch release data submitted in your response to Item 10 (refer to Table 4-5 on pages 38-40), submit a revised data report which addresses the following:
 - a. Provide actual results for biological activity testing.
 - b. Report each individual impurity at or above 0.05%, identify each impurity at or above 0.10%, and qualify each impurity at or above 0.15%, as requested in Item 11b of our February 11, 2005, letter. Also, refer to our comments on the impurity qualification report (Item 2 in this letter).
 - c. We note significant batch-to-batch variability in the amount of (b) (4) (b) (4) present in the drug product at release, i.e., none detected for batches SURF-0042 and 5075204, (b) (4) for batch 5085206A and (b) (4) for batch 5065202. Provide an explanation with an analysis of manufacturing changes responsible for these variations and implement adequate controls to remedy the problem.
 - d. We note a relatively high variability in results at release for (b) (4) (b) (4) and particle size distribution reported for the above batches. Investigate and explain the observed variation, and report your corrective actions to assure greater batch-to-batch consistency.
9. Item 11 in our letter dated February 11, 2005, remains a deficiency. We note you provided two different versions of Table 11-1 titled "Revised Drug Product Specifications" on pages 64-65 in volume 1 and pages 170-171 in volume 8 of the October 5, 2005, submission.
 - a. Provide one drug product specifications table with specified number and version, effective date, supersede date, and signed by the responsible individual. Clarify footnote 2 stating that "any impurities resulting exclusively from drug substance carryover *should* be listed on the certificate of analysis for reference only, and *should not* be included as a part of the calculation for the drug product related substances." Note that each impurity should be reported as a percentage of the parent drug substance and total impurities should reflect the capabilities of each analytical method – also refer to Item 11b from our February 11, 2005, letter.
 - b. We note that data provided in Table 11c-3 (page 78, volume 1) in support of the proposed acceptance criteria vary from the data presented for the same batches in Table 4-4 and 4-5 (pages 35-39, volume 1). For example particle size distribution for validation batch 5085206A is reported as (b) (4) (b) (4). Also, the (b) (4) content is slightly different, (b) (4) and colorimetric measurements vary as well (b) (4). Explain this discrepancy and state if the batch was re-processed.

- c. Tighten the proposed acceptance criteria to reflect the actual data, and report, identify, and qualify each impurity as requested in Item 11 of our letter dated February 11, 2005. Also, refer to our comments (Item 2) in this letter regarding the impurity qualification studies.
 - d. Your response to Item 11f remains deficient. Refer to our comments below regarding the analytical method for testing the biological activity of the drug product.
 - e. We acknowledge your agreement to further investigate the variability in drug product viscosity, as tested during release and stability, and implement corrective process controls as needed. Submit an updated report.
 - f. Revise the acceptance criteria for foreign particulates based on the submitted reports. Include the short description in the specifications table and tighten the numbers accordingly.
10. Item 12 in our letter dated February 11, 2005, remains a deficiency. We have the following remarks which may be helpful in addressing this deficiency.
- a. As requested in Item 12c, include a reference standard in your testing for drug product bioactivity and justify the appropriateness of your selection. The standard batch should be equivalent to batches used in the pivotal clinical trials with proven potency. In addition, justify your proposed positive criteria of a (b)(4) increase of Crs over control in your submitted protocol. Your proposal fails to meet our recommended criterion for positive Surfaxin bioactivity of $\geq 200\%$ (3-fold) increase of Crs over control ($p < 0.05$).
 - b. Regarding your response to Item 12d, incorporate a specified time for data collection into the methods for evaluating bioactivity for all future batches of the to-be-marketed product. The timing interval reported for studies to support the NDA (20-second intervals every 2 minutes for 30 minutes) is acceptable.
 - c. Regarding your response to Item 12e, it appears that the additional hypothesis test, incorporated to ensure adequate statistical power and to be conducted at "tier 2," will inflate the overall type I error. Explain how the type I error is controlled by the approach described in your response to Item 12e.
11. As requested in Item 13 in our letter dated February 11, 2005, provide a detailed impurity profile for the drug product, as detectable by each analytical method. Submit tables listing all detectable impurities and corresponding amounts of impurities analyzed for typical drug product samples tested during release and stability. Include corresponding chromatograms to facilitate the review. Revise the validation report for method D-021 to include LOD and LOQ levels.
12. Item 14 in our letter dated February 11, 2005, remains a deficiency. Provide analyses of complete data with numerical results for all impurity attributes and biological activity, as requested. We note that the release data, as summarized in Table 14-1, indicate a wide variability of the results for impurities, particle size distribution, surface tension, viscosity, and

foreign particulate matter. Address this issue by implementing adequate controls and/or changes to the manufacture or analytical methodology, as needed, to assure adequate batch-to-batch reproducibility.

13. Regarding your response to Item 15 in our letter dated February 11, 2005, provide revised specifications for [REDACTED] ^{(b) (4)}, which include detailed impurity profiles and a full list of the corresponding analytical methods. Also, refer to our Item 1 in this letter.
14. Submit a revised method validation (MV) package based on your resubmission to this NDA, for the drug substance and drug product. Include full validation for all non-compendial methods that are used for the analysis of drug product ingredients and drug product. Provide contact information for the validation samples. Submit three copies of the revised package to the NDA.
15. Item 18 in our letter dated February 11, 2005, remains a deficiency. Provide complete stability data with numerical results for all impurity attributes and biological activity, as requested.
16. In view of the multiple batch failures for sterility and/or biological activity testing, provide a comprehensive table listing all clinical batches, their manufacturing dates, the name of the manufacturer, and the start and end dates of their clinical use.
17. Regarding your response to Item 19 in our letter dated February 11, 2005, we note that the controls and analytical methods for drug substance and drug product are under continuous development during the progress of the NDA review. Submit a comprehensive response to our comments when the drug product manufacturing process and all analytical methods for drug substance and drug product are fully developed and validated.
18. Provide a revised stability protocol that includes a full impurity profile (refer to Item 2 in this letter) as requested in Item 21 of our letter dated February 11, 2005. Retain both storage orientations as previously requested. Include stability statements provided on page 124 as a part of the revised protocol. Also, provide a protocol number, effective date, supersede date, and authorizing/responsible official names. In view of the multiple failures for sterility and biological activity observed for drug product stored under labeled conditions, we do not recommend reduced frequency of testing for these attributes. Also, note that a test for sterility is required at the end of the expiry period.
19. Item 22 in our letter dated February 11, 2005, remains a deficiency. Provide a revised report with analysis of all available data obtained in both storage orientations, and address the following comments.
 - a. We note a high variability in the results for drug product biological activity, even at release for recently manufactured validation batches. Investigate the problem and implement adequate changes to the drug product manufacture process and/or the analytical method, as needed, to assure batch-to-batch reproducibility.

- b. A pattern of decreased lung compliance, or failures for either the lung compliance or the *p* value, is observed for the drug product samples stored in the upright position in comparison to the samples stored in the inverted position. For example, for batch SURF-0034 stored at 5°C, reported values at 6 months are 686 % inverted and 215% upright. Similar results at 12 months are 401% inverted and 319% upright. In addition, many results for the upright storage conditions are missing from your report, i.e., 3-month data points for each batch and 18-month data points for SURF-0034 and SURF-0035 are not reported. Provide a thorough explanatory report including the re-assessment of the integrity of the container closure.

20. Regarding your response to Item 23 in our letter dated February 11, 2005, provide the following:
 - a. An updated report on the changes observed in drug product activity and change in physicochemical properties with the increase of the amount of (b) (4). Provide supporting data collected with adequately validated methods. Retain separate acceptance criteria for the (b) (4), instead of the revised proposal to report all (b) (4) together.
 - b. Provide data characterizing physicochemical properties of the (b) (4) and evaluate possible changes in the peptide (b) (4). Explain the formation of (b) (4) with different rates for different batches.
 - c. Submit data on the content of (b) (4) in clinical batches at the time of use in the clinical trials.
 - d. Provide adequate qualification data on the (b) (4). Refer to Item 2 in this letter.

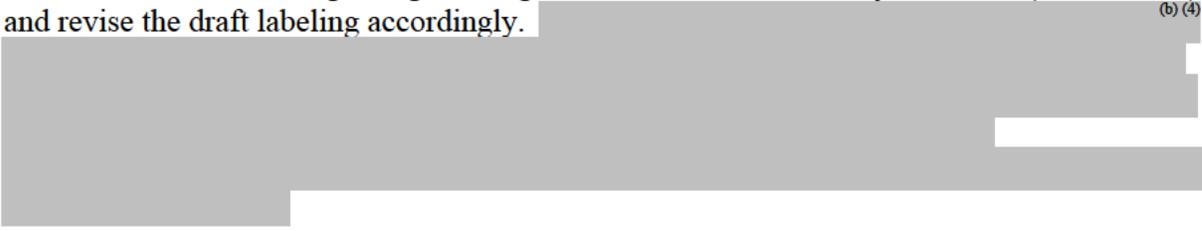
21. Regarding your response to Item 24 in our letter dated February 11, 2005, provide an updated comprehensive analysis of mass balance data upon implementing adequate changes to analytical methods and testing protocols. Although we note an improvement from previous reports, the mass balance results remain unacceptable, especially during stability testing.

22. Item 26 in our letter dated February 11, 2005, remains a deficiency. The currently submitted stability data do not support your request for a (b) (4) expiry period.

23. Item 33 in our letter dated February 11, 2005, remains a deficiency. Provide data supporting the storage of the drug product at 44°C for 8 h. We note a failure for biological activity for *p* value observed after 4 h at 50°C. Also, provide the description as to how to warm the drug product, e.g., water bath versus microwave, as requested. Emphasize the statement that vials are for single use only and the remaining portion of the drug product should be discarded.

24. Item 34 in our letter dated February 11, 2005, remains a deficiency. Provide a justification for warming the drug product to precisely 44°C, since this is not practical to attain and control in the environment of the delivery room.
25. Our field investigator could not inspect your Totowa facility last fall (i.e., following your October 5, 2005, submission) because the facility was not ready for inspection. This site is currently undergoing inspection. Satisfactory inspections of all facilities, including Totowa, are required before this application may be approved.

In addition, submit revised draft labeling that addresses the following preliminary comments:

26. The statement provided in your response to Item 35 in our letter dated February 11, 2005, is adequate; however, it should be duplicated on the carton and vial labels.
27. Regarding your response to Item 36 in our letter dated February 11, 2005, we have the following comments.
 - a. Emphasize throughout the label (i.e., package insert, and carton and immediate-container labels) statements about drug product sensitivity to light and advise protection from light exposure, since failures for peptide assay are evident as early as 4 hours after photoexposure at ICH Q1B conditions.
 - b. Emphasize warnings throughout the label (i.e., package insert, and carton and immediate-container labels) not to return the unopened, but warmed, drug to the refrigerator, and to discard the unused portion of the drug, since failures for biological activity are evident during the temperature-cycling studies.
28. Refer to the comments regarding labeling in our letter dated February 11, 2005, (Items 28-36) and revise the draft labeling accordingly. (b) (4)

29. Change  ^{(b) (4)} to "synthetic" in the DESCRIPTION section of the package insert.
30. Include the percent incidence of each of the most common adverse events (e.g., pallor, endotracheal tube reflex, endotracheal tube obstruction) associated with Surfaxin.

We reserve further comment on the labels and labeling until the above deficiencies are satisfactorily addressed.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

We note that a substantial number of serious deficiencies remain after two review cycles of your NDA. We encourage you to request a meeting with the Agency to discuss in detail your plans concerning the further development of your drug product.

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

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Robert Meyer
3/31/2006 04:10:56 PM



NDA 21-746

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

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

Dear Ms. Tsokas:

Please refer to your new drug application (NDA) dated and received April 13, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Surfaxin (lucinaactant) Intratracheal Suspension for use in ^{(b) (4)} respiratory distress syndrome (RDS).

We acknowledge receipt of your submissions dated April 27, June 15 and 29, July 1, August 16, September 13 and 30, October 8 and 19, November 1, 3, 5, 15, 17, 23, and 29, and December 1, 8, 17, 20, 28, and 29, 2004, and January 4, 6, 10, 12, and 31, 2005.

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

The following comments pertain to the drug substance.

1. Submit revised acceptance criteria (specification sheets) for verification testing of the incoming drug substance components (refer to Section 3.2.S.4.1). In your response, provide a complete list of tested attributes, analytical methods, and appropriate acceptance criteria for individual and total impurities for each drug substance component, ^{(b) (4)}
^{(b) (4)} In addition, provide characterization data for the sinapultide peptide. See additional comments below, which may be helpful in addressing this request.
 - a. List all identified, specified and unspecified individual impurities detected by each analytical method. Report each individual impurity present at or above 0.05%. Identify and limit individual impurities present at or above 0.10%. Qualify individual impurities present at or above 0.15%.
 - b. Submit a validated method for detecting impurities at the recommended levels (refer to the comment above and recommendations in the ICH Q3A guidance) and tighten the proposed acceptance criteria for each individual and total impurities detectable by each method.

- c. Include appropriate attributes that characterize and control the secondary structure of the peptide within the acceptance testing specifications for the sinapultide, e.g., circular dichroism with appropriate limits.
 - d. Tighten the acceptance criteria for (b) (4) impurities (b) (4) to reflect the data.
 - e. Indicate your proposed frequency of testing for each attribute listed on the specification sheets. Also, identify the responsible party, e.g., footnotes in the table explaining that test x is conducted on every batch of the incoming drug substance component by Discovery Laboratories. Explain the meaning of footnote #1: "Retest criteria" in the specification tables pertaining to the drug substance components.
2. Provide acceptance testing results collected according to the revised specifications and methods (refer to Comment #1 in this letter) for the recently used batches of drug substance components. Specify batch numbers for the corresponding drug product batches.
 3. The Drug Master Files (DMFs) supporting manufacture and controls of the drug substance components are deficient. This application cannot be approved until all deficiencies are addressed adequately by the DMF holders. Any complete response to this letter must include a statement that the DMFs listed below have been updated with a complete response to all deficiencies and list the dates each DMF was amended to correct the conveyed deficiencies.

- a. (b) (4)
- b. (b) (4)
- c. (b) (4)
- d. (b) (4)

The following comment pertains to the pharmaceutical development and drug product manufacture and packaging.

4. Since we note that changes have been implemented to the drug product container closure intended for drug product marketing, provide detailed information about these changes and submit appropriate data, e.g., appropriate comparative characterization, release, and stability data regarding extractables, leachables, and compatibility (e.g., potential adsorption of drug substance components). Provide revised letters of authorization (LOA) to the appropriate DMF(s), as needed.
5. The following comments pertain to the compatibility studies.
 - a. Submit data demonstrating compatibility between the drug product formulation and all contact surfaces during a validated manufacturing process.

- b. Submit data demonstrating compatibility of the stoppers intended for drug product marketing with the drug product formulation. Include information about the level of (b) (4). Assess changes in the physicochemical properties and biological activity of the drug product, resulting from the contact of the drug product suspension with stoppers during manufacture and upon storage in different vial orientations.
 - c. Provide data demonstrating compatibility of the drug product with the syringes and tubing systems that are commonly used to administer the drug product. Describe the contact parts of the equipment in detail, specify the names and addresses of the manufacturers and include information on whether the parts (b) (4). Assess changes in the physicochemical properties and biological activity of the drug product formulation upon contact with syringes and tubing commonly used for the drug product administration.
6. This application may not be approved until all sites, including (b) (4) and Laureate Totowa, involved in the manufacture and testing of drug substance and drug product have an acceptable recommendation from the Office of Compliance.
7. The following comments pertain to the sterile process validation and microbiology controls for manufacture of the drug product.
 - a. Provide a rationale for including only (b) (4) of the drug product manufacturing process, before the (b) (4). Note that we strongly discourage the use (b) (4). (b) (4) Revise the relevant standard operating procedures (SOPs) accordingly.
 - b. The proposed in-process controls (refer to Section 3.2.P.3.4) do not assure sterile manufacture of the drug product. We note that no in-process evaluation of bioburden, endotoxin, or sterility testing is carried out. Provide the revised list of the in-process controls and the name and address of the individual responsible for the overall assurance of the sterile drug product manufacture.
 - c. Revise the flow diagram for the manufacturing process to reflect the split of the manufacturing process between the two manufacturing sites, i.e., Laureate Totowa and Laureate Princeton. Describe the role of each facility in the process flow, i.e., where the process ends at Princeton and where it begins at Totowa. Provide overview of adequate SOPs assuring full control of the acceptance testing and the transport between the two sites. Evaluate the impact of the process split between the two manufacturing sites, including the possibility of manufacturing errors and overall assurance of sterility during sterile-fill manufacturing.
 - d. Clarify the contradiction in the results of the second set of media fills (February 2004). Data submitted in the NDA indicate that all three batches (FIL020C01, FIL020C02, and FIL020C03) in the media fill run had passed, whereas data submitted to DMF (b) (4) indicate that batch FIL020C03 was aborted due to a leak in the process equipment. Subsequently, batch FIL020C03 was replaced with batch FIL020C04 which passed the media simulation.

- e. Provide the investigative report describing the source of the contamination (*Bacillus thuringiensis*) found in the media fill batch FIL020B03, and other batches as applicable. Describe in details the corrective actions implemented to assure adequate process compliance in the future for this high-risk profile drug product.
 - f. The original referenced DMF (b)(4) did not contain the pertinent manufacturing information. The DMF holder was advised of this fact, and they provided reference to a second, DMF (b)(4) and submitted an amendment on December 13, 2004. DMF (b)(4), which supports the sterile process validation and microbiology controls for manufacture of the drug product, was not reviewed for this action. You may incorporate this submission by specific reference as part of your complete response to deficiencies cited in this letter.
8. Justify the reason for the (b)(4) used routinely in batch formulation and the (b)(4) used in the formulation of batch SURF-0035. In your response account for (b)(4) during manufacturing.
 9. Provide a complete list of all drug product excipients, the names and addresses of the currently used manufacturers/suppliers, and copies of the acceptance criteria for the incoming materials.
 10. We note that the NDA batches were manufactured prior to the successful media fill and prior to qualifying the manufacturing equipment. Submit release and available stability data for batches manufactured with a validated manufacturing process and filled to the container closure intended for marketing. Refer to our comments on the proposed drug product specifications below for data collection and presentation.

The following comment pertains to the drug product specifications.

11. Submit revised Specifications sheet for the drug product, addressing the following comments. The table format, as submitted in Section 3.2.P-14 of the original application, is preferred to facilitate a comprehensive and accurate assessment. Attach a sheet listing chemical names and structures for all known impurities.
 - a. Substantially tighten the proposed release and stability criteria for assay for each active ingredient, or demonstrate that changing the proportion of active ingredients, i.e., varying the drug product formulation within a 35% range for sinapultide, DPPC, and POPG, does not change the potency and activity of the drug product. Specify the acceptance criteria as a target value for each ingredient, followed by a range of mg/mL values and a percentage range.
 - b. As noted in our letter dated June 25, 2004, the proposed acceptance criteria for drug product impurities are unacceptably wide, e.g., (b)(4) for individual unknown, and (b)(4) for total unknown impurities, depending on the method. Revise the drug product impurity/degradants specifications to list all individual impurities, i.e., identified, specified, and unspecified. Report all individual impurities occurring at or above 0.05%, identify each impurity present at or above 0.10%, and qualify each impurity present at or above 0.15%. The synthetic/process impurities (b)(4) which do not increase during drug product manufacture or storage, do not need to be monitored on release or stability but should be listed on the specification sheet for a reference. Revise the analytical methods for impurities and decomposition products

as needed and tighten the acceptance criteria accordingly to the results. Provide statistical evaluation of data and justification for the proposed limits.

- c. Tighten the proposed acceptance criteria for appearance (colorimetric), ^{(b) (4)} and particle size distribution (PSD) tests. Express acceptance criteria for ^{(b) (4)} in parts per million (ppm). Provide results for batch release and shelf-life testing to justify the proposed acceptance criteria.
 - d. Provide the results of the investigation of the high variability in the drug product viscosity, i.e., batch results varying from ^{(b) (4)}, at release. Summarize the actions taken to avoid such variations in the future. Provide adequate controls for the incoming drug product ingredients, manufacturing process, and release and stability testing to assure adequate reliability of the drug product viscosity. Tighten the drug product specifications accordingly.
 - e. Revise the proposed acceptance criteria for the drug product volume in container to include a target value, followed by the acceptable limits in milliliters per vial.
 - f. Revise the acceptance criteria for the *in vivo* activity of the drug product to include changes with time in tidal volume and lung thorax compliance for the tested rabbits. Also, refer to the specific comments below regarding the analytical method.
 - g. Include the dose content uniformity results in the routine release and stability testing of the drug product.
 - h. Submit a report on the nature and origin of the high levels of foreign particulates in the drug product. Revise the method and acceptance criteria to include the load of particles per vial, in each size group. Include a brief description of particles in the specification table.
12. The following comments pertain to the analytical method DP-018 for testing of the biological activity of the drug product. Submit a revised method, method validation and revised acceptance criteria addressing the following comments.
- a. Determine the acceptance criteria of the lung immaturity for each animal using a specific tidal volume under a specific pressure after stabilization.
 - b. Test the control animals untreated rather than giving Tris saline buffer, since the saline treatment is known to decrease lung compliance.
 - c. Include an internal reference standard of Surfaxin (e.g., the batch used in the pivotal clinical trials, or an equivalent batch of proven potency). The internal standard is expected to show a statistically significant increase of Crs \geq 200% of the mean control value. If the increase is less than 200%, appropriate justification should be provided.
 - d. Collect data for the tidal volume and lung compliance at specific time points rather than in ranges of 2-5 minute intervals. Submit all data at predetermined time points to support the proposed acceptance criteria.
 - e. Increase the number of animals to be tested to at least 6 per group, with randomization employed among each litter.

13. Provide a detailed impurity profile for the drug product with a thorough summary of the potential process impurities and degradation products. Revise the analytical methods DP-001, DP-017, and DP-019 and the corresponding validation reports to provide information and data demonstrating that the methods are capable of detecting and quantifying all process impurities and degradation products. Demonstrate the specificity and selectivity of the methods and provide the limits of detection and quantification for all process and degradation impurities. Include copies of adequately marked chromatograms of the standard solutions, drug product solutions, and drug product solutions spiked with the impurity standards.
14. Submit comprehensive data analyses for drug product batches manufactured according to a validated manufacturing process. Provide data for all testing attributes including detailed impurity profile and biological activity of the drug product.
15. The following comments pertain to the Reference Standards for drug product purity.
 - a. Provide revised acceptance criteria for the sinapultide standard that assures adequate purity of the peptide (e.g., NLT 98%) and that will confirm and control the secondary structure of the peptide, e.g., circular dichroism method with appropriate acceptance criteria.
 - b. Provide a complete list of manufacturers, tests, and acceptance criteria for all incoming standards that are used to characterize impurities present in the drug substances and drug product.
16. Provide specification sheets for the acceptance testing of the incoming container closure components. Include methods, acceptance criteria, and data to confirm results from the certificates of analysis (COA).
17. Submit the method validation (MV) package based on your resubmission to this NDA for the drug substance and drug product. Include full validation for all non-compendial methods that are used for the analysis of drug product ingredients and drug product. Provide contact information for the validation samples. Submit three copies of the revised package to the NDA.

The following comments pertain to the drug product stability studies.

18. Submit results of the stability data from drug product batches manufactured with a validated manufacturing process. The data should be collected for all test attributes including the revised biological activity, dose content uniformity, and detailed impurity profile.
19. Submit all available stability data for drug product batches SURF-0029, SURF-0031, SURF-0034, and SURF-0035, to include the full impurity profile - refer to comment 11 in this letter. Explain the discrepancies between the data for individual and total impurities submitted to this NDA and the data on file at the drug product testing facility. For example, the NDA stability report, submitted October 19, 2004, for batch SURF-0034 (manufactured November 7, 2003, and stored upright at 5°C for 6 months) includes three individual unknown impurities at (b) (4) total unknown impurities at (b) (4) and total impurities at (b) (4). However, records at the testing facility indicate (b) (4) for one individual unknown impurity for the same batch at the

- same data point. Data from the testing facility reflect that this unknown impurity is present in all drug product batches, and increases up to levels of (b) (4) upon storage for 30 months at 5°C. These data were not submitted to the NDA. Identify and provide the structure of this impurity, and provide a comprehensive report addressing the discrepancies in the data reported to this NDA.
20. The submitted stability data from the photostability study, the temperature-cycling study, the short-term (24 h, 50°C) stability study, and the storage-in-the-syringe study are incomplete. Submit appropriate results for all stability test attributes for these studies.
 21. Revise the drug product stability protocol to address our comments regarding stability attributes, acceptance criteria, and testing methods. Specify that any extension of the expiry will be based on the full shelf-life stability data. Submit one Stability protocol upon implementing the requested changes that will apply to all post-approval batches.
 22. Submit all available release and stability data for the drug product biological activity from samples stored in upright and inverted positions. Refer to our (b) (4) comments above regarding the analytical method.
 23. Provide comprehensive analyses of any instability trends occurring in the drug product upon storage, in relation to the drug product activity. Explain the formation of (b) (4) (b) (4) with different rates for different batches and storage conditions. Provide the structures of the (b) (4) and evaluate the impact of formation of (b) (4) on the drug product activity.
 24. We note that assay results for drug substances components indicate a decrease of the active ingredients of up to 17% for sinapultide, 11% for DPPC, and 19 % for POPG, and an increase of up to 30% for PA upon storage. However, the few impurities that are reported, for the recent batches only, do not account for the mass balance loss of the active ingredients. Evaluate the adequacy of the analytical methods to monitor impurities and provide a mass balance analysis, with comprehensive supportive data, for the changes occurring in the drug product during storage.
 25. We note an abrupt increase in the drug product surface tension after 12 months of storage under the label conditions. The increase correlates with changes in the particle size distribution of the drug product. Evaluate the impact of those changes on the (b) (4) structure and activity of the drug product. Provide any appropriate supporting data.
 26. The currently submitted stability data do not support your request for (b) (4) expiry for the drug product. Comments on the drug product expiry period are reserved pending resolution of the outstanding deficiencies in drug product manufacture and review of the adequately collected and reported stability data. Refer to our comments above.

The following comment pertains to your clinical development program.

27. We note that no assessment of immunogenicity was performed during the clinical studies. Submit an adequate justification of why immunogenicity assessments were not performed during the clinical program or, alternatively, submit adequate immunogenicity assessment data from Surfaxin use.

In addition, it will be necessary for you to submit draft labeling incorporating the following preliminary comments. Additional labeling comments will be provided upon the review of your

full response to the deficiencies listed in this letter and our letters to holders of the referenced DMFs.

28.

(b) (4)
[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Drug Products regarding the extent and format of your safety update prior to responding to this letter.

A response to this action letter will be considered complete only when all deficiencies from this letter, and from all supporting DMFs, are adequately addressed.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

In addition to the above deficiencies, we have the following comments regarding your post-marketing plans. While not approvability issues, we would appreciate a response to these comments in your complete response.

A. [REDACTED] (b) (4)

B. We note that no dose-ranging studies were performed for a prevention indication. We also note that in the pivotal study there was a higher incidence of negative reactions to dose administration for Surfaxin than for other surfactants. The increased risk of negative reactions to dose administration found in the pivotal study may be related to the larger volume per dose of Surfaxin. While we acknowledge the challenges in clinical dose-ranging in the circumstances of neonatal RDS, additional clinical dose-ranging information,

particularly of lower doses, would help determine whether negative reactions to dose administration could be reduced without affecting efficacy.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

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

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Robert Meyer

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