CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021746Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	March 6th, 2012
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology, Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-746
Applicant Name:	Discovery Laboratories, Inc.,
Date of Submission:	September 6, 2011 (original submission was on April 13, 2004)
PDUFA Goal Date:	March 6, 2012
Proprietary Name:	Surfaxin
Established Name:	Lucinactant
Dosage form:	Intratracheal Suspension
Strength:	Recommended dose is 5.8 mL per kg birth weight every 6 hours up to 4 doses in the first 48 hours of life
Proposed Indications:	Prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk of RDS.
Action:	Approval

1. Introduction

This is the fifth review cycle for Surfaxin (lucinactant) Intratracheal Suspension (NDA 21-746), which was originally submitted by Discovery Laboratories on April 13, 2004. Surfaxin, like other surfactants for the prevention or treatment of RDS in premature infants has an orphan designation. The original application included the results of a single pivotal study (study KL4-IRDS-06) that established the efficacy and safety of lucinactant for the proposed indication of the prevention of RDS in premature infants at high risk of RDS. The clinical recommendation for the original submission was Approval; however, there were and continued to be major CMC deficiencies that led to complete response actions on previous review cycles. These have included drug substance related impurities for (b) (4) that exceed the qualification threshold of 0.15% recommended by the ICH guidance Q3A, and major deficiencies related to inadequate specifications for release and stability, inadequate information on the drug product manufacturing process and repeatedly deficient GMP status, inadequate stability data, inadequate acceptance criteria for impurities, and inadequate validation of the lucinactant bioassay to be used for drug product release and stability testing. Over the course of the previous four review cycles, most of the CMC deficiencies have been resolved. The last outstanding CMC issue that Discovery addresses in this submission is the lack of a validated bioassay to demonstrate biological activity of the drug. This is a critical element in the development of locally active surfactant products as it is used to establish the release specifications and guarantee the consistency and quality of new batches of a life-saving drug for use in critically ill premature infants. In the past, Discovery has been unable to demonstrate the ability of their bioassay in a fetal rabbit model of RDS to differentiate lucinactant activity between

the inactive (expired) and active (unexpired) batches or lots of drug product. This review will briefly describe the Surfaxin development program and the fetal rabbit bioassay to demonstrate biological activity of the drug.

2. Background

Surfaxin is a new molecular entity by virtue of the constituent sinapultide, a unique synthetic peptide of 21 lysine and leucine residues. Natural mammalian lung surfactant contains at least four constitutive proteins designated surfactant-associated proteins A, B, C, and D (abbreviated SP-A, SP-B, SP-C, and SP-D). Of the four proteins, SP-B appears to play a major role in reducing alveolar surface tension. Sinapultide is intended to mimic the structural and functional properties of SP-B. Surfaxin also contains phospholipids intended to mimic the characteristics of the phospholipids in native surfactant, since SP-B activity depends on the presence of surface active phospholipids.

Neonatal RDS develops when birth occurs prematurely before full development of the pulmonary surfactant system. Without surfactant, the lungs collapse at the end of expiration resulting in generalized atelectasis, which leads to respiratory failure accompanied by several complications. In untreated patients, neonatal RDS result in high morbidity and mortality. Over the past decade several exogenous surfactants have been developed to prevent and treat neonatal RDS (Table 1). Of the four surfactants approved in the United States, Survanta, Infasurf, and Curosurf are animal derived, and Exosurf is synthetic. Surfaxin, the subject of this application, is a synthetic surfactant. The initial surfactant product marketed, Exosurf, was synthetic and lacked a protein component while the other products are derived from animal (bovine or porcine) lung surfactant and standardized for protein and phospholipid content. Initial concerns over potential immunogenicity and transmission of infectious diseases for the animal-derived products have not been realized in the approximately 22-year history of their use.

Table 1. Surfactant Products in the United States

Product	**NDA number Approval date**	**Product Information**	**Indication**
Exosurf*	NDA 20-044 August 1990	**Synthetic** Colfosceril palmitate 13.5 mg/mL; tyloxapol; cetyl alcohol	Prevention Treatment
Survanta	NDA 20-032 July 1991	**Bovine** Phospholipids 25 mg/mL; SP-B <0.2 mg/mL	Prevention Treatment
Infasurf	NDA 20-521 July 1998	**Bovine** Phospholipids 35 mg/mL; SP-B 0.26 mg/mL	Prevention Treatment
Curosurf	NDA 20-744 November 1999	**Porcine** Phospholipids 80 mg/mL; SP-B 0.3 mg/mL	Treatment
Surfaxin	NDA 21-746 Pending	**Synthetic** Phospholipids 30 mg/mL; sinapultide 0.8 mg/mL	Prevention
* Not marketed in the United States since 2001.			

Historically, the use of surfactant in the management of neonatal RDS involved two strategies, prevention and treatment. In the prevention strategy, surfactant is

administered as soon as feasible after birth in high-risk premature infants (generally 32 weeks or less of gestational age and 1250 gm or less of body weight) to prevent the development of neonatal RDS. In the treatment strategy, surfactant is administered to neonates who did not receive preventive surfactant and developed RDS during the first day of life. Of the four surfactants approved in the United States, Exosurf, Survanta, and Infasurf have both prevention and treatment indications, and Curosuf has only the treatment indication (Table 1). The applicant is seeking only a prevention indication for Surfaxin. The first dose of Surfaxin is proposed to be given (b) (4) (b) (4) Up to three additional doses are proposed to be given at minimum six-hour intervals if RDS develops. Since the strategy is prevention, it is likely that some infants will receive Surfaxin who would not have developed RDS. The clinical program conducted by the applicant to show efficacy and safety of Surfaxin consisted of one pivotal study. The results of the study, along with supporting clinical data, support the efficacy and safety of Surfaxin.

Because surfactant drug products are locally active at the alveolar air/liquid interphase and their activity is (b) (4) of the peptides in the drug monolayer that is formed at the site of action, drug lots of surfactant products are subject to a bioassay (typically performed in rat or rabbit pup lungs) prior to lot release in order to demonstrate biological activity in reducing surface tension with a resultant increase in lung compliance. These bioassays should be developed at or before the time that pivotal clinical studies are performed in order that the assay procedure can be linked and thereby validated, to the performance of the clinical lots demonstrated to be effective in the clinical studies conducted to support approval of the surfactant product. One of the major problems with the rabbit model bioassay proposed by Discovery for the determination of biological activity for Surfaxin has been that it was not developed until after the pivotal clinical trials were conducted and no original drug product remained and therefore has not been able to be linked to the biological activity and subsequent clinical efficacy demonstrated in the pivotal clinical trial. The problem of the lack of a validated bioassay that could be linked to the clinical efficacy of the drug lots used in the pivotal clinical study is further compounded by the significant changes made in the manufacture of Surfaxin since the clinical trials were conducted for the RDS indication and has remained a major issue that would need to be resolved prior to approval.

This issue has been conveyed to and discussed with Discovery on multiple occasions during the clinical development of Surfaxin. Discovery subsequently acknowledged that no batches used in the clinical trials were available to be used as an internal standard to validate the proposed bioassay however, and it was discovered that an animal study was conducted with the original clinical trial material in a fetal lamb model of RDS which demonstrated some degree of biological activity (approximately a 150% increase in lung compliance; Pediatrics 2006, vol 117:295-303). At a meeting held on December 21, 2006, the Division agreed to allow the lamb model to be used as a bridge to the efficacy demonstrated in the clinical lots of Surfaxin provided that currently manufactured lots of Surfaxin were found to demonstrate a similar degree of biologic activity when administered to fetal lambs in a manner comparable to the methods used in the published study. The Division then stated that since the lamb model demonstrated the bioactivity of

the batches used in pivotal clinical trials, to be validated, the rabbit model should show comparable bioactivity to the lamb model. In subsequent submissions, Discovery has demonstrated that the currently manufactured drug product has comparable bioactivity to the drug product used in the pivotal clinical trial in the lamb model but has been unable to demonstrate that the proposed rabbit bioassay shows comparable activity to the lamb model. In short, the rabbit bioassay lacked sensitivity and, unlike the lamb assay, was not able to capture the loss of drug activity over time due to degradation and loss of the synthetic (b) (4) in drug product that had gone beyond its expiration date. The current submission addressed these deficiencies.

3. Chemistry, Manufacturing, and Controls

The drug product is an aqueous suspension of sinapultide, a synthetic peptide of 21 lysine residues and a mixture of synthetic phospholipids [(dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG), and palmitic acid (PA)]. While phospholipids are common to all surfactant products, the sinapultide peptide is designed to simulate the function of natural surfactant proteins which are present in the currently marketed surfactant products made from animal lung extracts. The drug product is sterile-filled to 10 mL sterile glass vials and contains 0.86 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG, and 4.05 mg/mL of PA, in 8.5 mL per vial. This corresponds to a concentration of 30 mg of total phospholipids per each mL of drug product suspension. The commercial drug product will be manufactured by Discovery at their Totowa, NJ site.

The requested expiry period for the drug product is 12 months and it is supported by the submitted data. This is a rather short expiry period but it is the result of limited stability of the drug product due to a chemical reaction occurring between the active ingredients, notably, the (b) (4) All current DMFs have been judged as adequate.

A recent GMP inspection evaluating the 2011-implemented changes to the sterile fill process has been judged as adequate. In addition, GLP and GMP inspections at the sites where the testing for biological activity of the drug product using the rabbit bioassay is performed (b) (4) and raw data processed, reported, and interpreted (Discovery site, Warrington, PA) have been judged as acceptable with one caveat. While the data generated and analyses of the raw data were accurate, the inspectors noted a general lack of quality assurance oversight for the bioassay. One specific issue was that while the raw data are generated at (b) (4), the quality oversight is performed at Discovery in Warrington, PA. In order to assure better quality oversight, after discussion with Discovery, they have agreed to transfer quality assurance monitoring to the (b) (4) lab performing the assay. When accomplished, the company will submit a prior approval CMC supplement to the NDA which will likely generate a GMP inspection to assure adequate quality measures have been incorporated. This process will be documented as a post-marketing commitment by the company.

The importance of the analytical method evaluating the biological activity of the drug product (assessing drug potency in premature rabbits) is key for this application as it serves as a regulatory release and stability method for the drug product. In addition, by demonstrating comparable surface tension reducing activity to that of a lamb model of RDS, the rabbit bioassay is the bridge to link the bioactivity of the currently manufactured drug product to the drug product used in the pivotal clinical trial. After careful review and frequent interactions with the Applicant, the review team concluded that the rabbit bioassay had met the criteria for acceptable specificity, precision, range, linearity, and accuracy and was also comparable to the preterm lamb model in demonstrating loss of drug biological activity over time.

4. Nonclinical Pharmacology and Toxicology

The animal pharmacology and toxicology studies conducted for Surfaxin were somewhat limited because of the nature of the drug product and the fact that the drug is to be administered acutely over a period of at most, 48 hours. Animal pharmacology studies demonstrated that Surfaxin reduced surface tension in ex vivo systems; and increased lung compliance and expansion, improved gas exchange, and reduced ventilatory pressures in animal models of RDS. Animal toxicology studies were conducted in neonatal rabbits, neonatal dogs, and neonatal cats. The studies were characterized by respiratory distress in animals dosed, and early deaths in rabbits from pulmonary causes. Histopathology in repeat dose studies showed evidence of lung inflammation with lung histiocytosis and inflammatory cell infiltrates at all doses and as a result, NOAELs could not be established.. Clinical studies were allowed to proceed because of the intended clinical benefit, a decrease in RDS-related mortality. Reproductive and carcinogenicity studies were not performed for Surfaxin. Animal immunotoxicity studies in guinea pigs were performed and showed no evidence of a hypersensitivity response.

5. Clinical Pharmacology and Biopharmaceutics

Clinical pharmacology studies were not required to be conducted for Surfaxin because it is both administered and active locally and does not gain significant entry into the systemic circulation.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Discovery conducted four studies with Surfaxin in patients with neonatal RDS, of which one study (Study KL4-IRDS-06) was considered the pivotal study, and two studies (Study KL4-IRDS-02, Study KL4-IRDS-05) were supportive. Studies KL4-IRDS-06, KL4-IRDS-02, and KL4-IRDS-05 used the prevention strategy, which is relevant to the proposed indication. A fourth study (KL4-IRDS-01) used the treatment strategy and is

therefore not relevant to the proposed indication, but was the only study that used a range of doses of Surfaxin.

The doses and dosing regimens for the lung surfactant products including Surfaxin have mostly been derived empirically. This applicant selected an initial clinical dose of 133 mg/kg phospholipids based on results of primate studies. Later primate studies showed that a higher dose of 200 mg/kg produced more consistent and longer-lasting effects. A clinical dosing study (Study KL4-IRDS-01) then compared the two doses, but the study was in the treatment strategy and only eight patients received the lower dose.

The clinical program comprised of one pivotal study with other studies primarily providing supportive safety data was acceptable to the Division because of the nature of the indication and the difficulties in doing RDS studies given approved, lifesaving therapies already on the market. The single study was carefully designed in consultation with the division and the Office of Biostatistics. The applicant and the Division had multiple interactions during the development program of Surfaxin where the design of the pivotal study was discussed.

b. Design and conduct of studies

Study KL4-IRDS-06 was a multi-center, double-blind, active-controlled parallel group study conducted in premature neonates between 600 grams and 1250 grams birth weight. The study was conducted in 54 centers in Europe (Hungary, Poland, and Russia) and in Latin America (Brazil, Chile, Ecuador, Mexico, Panama, and Uruguay). Infants satisfying the entry criteria were randomized at a ratio of 2:2:1 to Surfaxin, Exosurf, and Survanta. Exosurf was considered the primary comparator, with Survanta included as a reference product. The hypothesis was that Survanta would be more effective than Exosurf, since the latter does not include an SP-B mimetic peptide. Patients were stratified within each category by birth weight. The first dose of surfactant was given between 15 and 30 minutes after birth and up to three subsequent doses could be given at 6-hour intervals if certain predefined criteria consistent with development of RDS were met. The study had two evaluation phases: the first phase was through 36 weeks post-conceptional age, hospital discharge, or death, whichever occurred later, and the second phase consisted of follow-up evaluations at 6 and 12 months corrected age. There were co-primary efficacy endpoints – incidence of RDS at 24 hours, and RDS-related death at 14 days. A seven-member adjudication committee adjudicated both endpoints. The adjudication committee decisions were used in the primary analyses. Secondary endpoints included all-cause mortality, occurrence of air leaks, development of bronchopulmonary dysplasia (BPD), severity of RDS, number of surfactant doses, duration of oxygen supplementation, ventilation, hospitalization, and occurrence of concurrent diagnoses. The presence of air-leak at 7 days was initially a part of the composite co-primary endpoint, but it was later removed from the co-primary endpoint by the applicant prior to unblinding of the efficacy data with the Division's concurrence. There were challenges in defining the co-primary endpoints and substantiating them in the clinical setting, but the applicant adhered to the agreed upon processes and carried them out with due diligence. Safety was assessed through adverse event reports, assessment for any negative reactions to dose administration, use of concomitant

medications, physical examinations, and vital signs. An event driven design was used to estimate the sample size based on published incidences of RDS and death for Exosurf-treated patients. With this scheme, 400 RDS events and 66 RDS-death events were estimated to be needed and this was anticipated to require 600 patients in the Surfaxin and Exosurf groups.

c. Efficacy findings and conclusions

The clinical program support efficacy of Surfaxin for the proposed indication of the prevention of RDS in premature infants at high risk of RDS.

Results of the primary efficacy variable and selected secondary efficacy variables from study KL4-IRDS-06 are shown in Table 2. Surfaxin was statistically significantly superior to Exosurf on the primary efficacy variables, and the secondary efficacy variables mostly tended in favor of Surfaxin. The results were consistent across populations based on birth weight, gender, and race. Surfaxin appeared similar to Survanta on these endpoints, helping to assuage concerns that this artificial product might be inferior to a naturally-derived surfactant. The non-RDS related death rate tended to be higher in the Surfaxin group compared to the other groups. This increase was primarily due to deaths from renal failure and from sepsis (Table 2). These two causes of death are difficult to relate to Surfaxin from a physiological or pharmacologic standpoint. It was reassuring that two other causes of death, intraventricular hemorrhage and pulmonary hemorrhage, which are considered to be physiologically related to RDS, favored Surfaxin. In the decisions of the adjudication committee, these two causes of death were frequently not counted under RDS-related death.

There were two safety issues that were of concern. The first was the suggestion of higher rates of infection-related events in Surfaxin treated patients including death from sepsis as discussed above. The second was negative reactions related to the administration of Surfaxin, which included obstruction of the endotracheal tubes and interruption and discontinuation of dosing. These reactions occurred most likely because the volume of Surfaxin was relatively larger compared to other surfactants. These reactions related to administration of Surfaxin have important clinical implications.

Table 2. Efficacy results, n (%)

	Surfaxin (n=527)	**Exosurf (n=509)**	**Survanta (n=258)**	**p-value**	
				vs Exosurf	**vs. Survanta**
RDS at 24 hr	206 (39.1)	240 (47.2)	86.3 (33.3)	0.005	0.108
RDS-related mortality through 14 days	25 (4.7)	49 (9.6)	27 (10.5)	0.001	0.001
Air leak at 7 days	80 (15.2)	89 (17.5)	35 (13.6)		
All cause mortality, day 14	84 (15.9)	86 (16.0)	48 (18.6)		
Alive and no BPD at 36 wk	313 (59.4)	274 (53.8)	144 (55.8)		
BPD at 36 wk	212 (40.2)	229 (45.0)	110 (42.6)		
Non-RDS related mortality	59 (11.2)	37 (7.3)	21 (8.1)		
Renal failure	7 (1.3)	1 (0.2)	0 (0)		
Sepsis	23 (4.4)	18 (3.5)	4 (1.6)		
Intraventicular hemorrhage	17 (3.2)	28 (5.5)	18 (7.0)		
Pulmonary hemorrhage	15 (2.8)	12 (2.4)	11 (4.3)		

The two supportive studies are briefly described below.

Study KL4-IRDS-02 was a multi-center, double-blind, active-controlled parallel group study conducted in premature neonates between 600 grams and 1250 grams birth weight. The study was conducted in centers in US, Canada, UK, and several European countries. Infants satisfying the entry criteria were randomized to Surfaxin or Curosurf. Patients were stratified within each category by birth weight. The first dose of surfactant was given between 15 and 30 minutes after birth and up to two subsequent doses could be given at 6-hour intervals if certain predefined criteria consistent with development of RDS were met. The study had two evaluation phases: the first phase was through 36 weeks post-conceptional age, hospital discharge, or death, whichever occurred later, and the second phase consisted of follow-up evaluations at 6 and 12 months corrected age. The primary efficacy endpoint was the incidence of being alive without BPD at Day 28 of life. Investigators determined whether BPD was present according to predefined criteria. Secondary endpoints included RDS at 24 hours, RDS related mortality at 14 days, all-cause mortality, occurrence of air leaks, bronchopulmonary dysplasia (BPD), severity of RDS, number of surfactant doses, duration of oxygenation, ventilation, hospitalization, and occurrence of concurrent diagnoses. Safety was assessed through adverse event reports, negative reactions to dose administration, concomitant medications, physical examination, and vital signs. The study was of non-inferiority design with a non-inferiority margin of -14.5% and a sample size of 248 patients per group was determined to be needed for the study. The selection of the non-inferiority margin is questionable because the margin was set based on results of only one limited treatment study comparing Curosurf to placebo and the primary endpoint was different than the one used in this study (Pediatrics 1988; 82:683-691). Therefore, the validity of the study for assessing definitive efficacy was questioned by the Agency even prior to its conduct. Of note, this study was terminated prematurely for business reasons, which further weakens its contribution to the efficacy assessment.

Results of the primary efficacy variable and selected secondary efficacy variables are shown in Table 3. Efficacy conclusions from this study are very limited because of reasons stated above. Surfaxin was generally well tolerated in this study.

Table 3. Efficacy results, n (%)

	Surfaxin (n=119)	**Curosurf (n=124)**
Alive without BPD at 28 days	45 (37.8)	41 (33.1)
RDS at 24 hr	22 (18.5)	19 (15.3)
All cause mortality at 14 days	13 (10.9)	17 (13.7)
Non-RDS related mortality	12 (10.1)	17 (13.7)
Air leak at 7 days	11 (9.2)	9 (7.3)
Alive and no BPD at 36 wk	77 (64.7)	84 (67.7)

Study KL4-IRDS-05 was a single-center open-label study conducted in 11 premature neonates in Ecuador to examine the logistics and feasibility of proceeding to larger studies. All patients were treated with 175 mg/kg of Surfaxin, half of the patients were to receive the doses in two half-dose aliquots and half of the patients were to receive the doses in four quarter-dose aliquots. Patients in the study were followed through 28 days and there was no long-term follow-up.

8. Safety

a. Safety database

The safety assessment of Surfaxin is based on the studies mentioned in section 7 above. The safety database is reasonable considering that RDS is an orphan disease.

b. Safety findings and conclusion

The safety data do not raise safety concerns in the RDS patients that would preclude approval or place any major limitation on the use of Surfaxin.

In reviewing the safety of Surfaxin compared to other active comparator surfactants (Survanta and Curosurf) used in the clinical studies in this critically ill population, it is clear that patients who received Surfaxin had a higher incidence of prospectively defined negative reactions to dosing (dose interruption, endotracheal tube obstruction, ETT reflux, pallor, etc.) than those who received other surfactant products. While this issue was not addressed by Discovery, the most obvious likelihood is that the larger dose volume of Surfaxin per kg of patient weight compared to other marketed surfactant products is responsible. This information will be mentioned in the product label.

While most of the other previously submitted safety update data available did not reveal any new safety issues, there was one notable finding of increased serious adverse reactions, including an increase in deaths and other serious adverse reactions in adults with ARDS who received high doses of Surfaxin via segmental bronchial lavage in study KL4-ARDS-04. Information about the increase in serious adverse reactions, including death, in adults with ARDS who received Surfaxin via segmental bronchial lavage will be mentioned in the product label.

Subsequent previous clinical submissions have consisted of safety updates for ongoing studies involving Surfaxin; however, none were conducted in the same study population for which this NDA applies (premature infants at risk for RDS). The study that was conducted in a population closest to the indicated population was Study KL4-BPD-01. This was a randomized, double-blind, placebo controlled, Phase 2 trial designed to evaluate the safety and efficacy of up to 5 doses of lucinactant in 136 very low birth weight premature infants between 3 and 10 days of life still requiring mechanical ventilation and at risk for developing bronchopulmonary dysplasia. For this study there was no new safety signals noted; the most common adverse reactions continued to be those related to surfactant administration and included hypoxia and bradycardia.

For this NDA cycle, the safety update contained unblinded safety data for the recently completed study, KL4-ARHF-01, a randomized, placebo-controlled study to assess the safety and efficacy of lucinactant (Surfaxin) in children up to 2 years of age with acute hypoxic respiratory failure. One hundred sixty five patients with hypoxemic respiratory failure were enrolled (Surfaxin = 84, sham air placebo = 81) to receive up to two 5.8 mL/kg doses of Surfaxin separated by at least 12 hours. The peri-dosing adverse reaction profile was similar to other Surfaxin studies, i.e., increased compared to placebo or alternative surfactant products. Another notable finding was that for the 7 deaths noted for the study, 6 were in Surfaxin-treated patients. Of the 6 patients treated with Surfaxin who died, 4 died from infectious disease (3 from pertussis, 1 from RSV) and the other 2 were from hepatitis with gram negative sepsis and a child with Down syndrome and pre-existing pneumonia. So, while a death imbalance was noted, the types of deaths which occurred were not consistent with an adverse Surfaxin treatment effect.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. After initial review of the data the Agency decided that the efficacy and safety were sufficiently clear and did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease, and there were no controversial issues that would have benefited from advisory committee discussion.

10. Pediatric

RDS is an orphan disease and not subject to PREA. In any event, indication (prevention of RDS) is in a narrow niche of the general pediatric population, i.e., premature infants at risk for RDS. Because this disease entity does not exist outside the premature infant population, no additional studies in other pediatric populations would be relevant to the indication.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited four study sites that participated in the pivotal study KL4-IRDS-06, the adjudication process of study KL4-IRDS-06, and the laboratory that conducted the animal toxicology study. The clinical study sites were selected because of high enrollment, high number of deaths, and/or inconsistencies in the cause of death determined by the investigator and the adjudication committee. Sites were selected to evenly represent the European and Latin American countries. The DSI audit concluded that all sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. Minor deviations were noted in some sites, but these were not of a magnitude that would impact the conclusions of the studies. During review of the submission, no irregularities were found that would raise concerns

regarding data integrity. Despite some history of ethical issues in discussion leading up to the pivotal trials, no important ethical issues were found in the final program. All studies were performed in accordance with accepted clinical standards.

b. Financial Disclosure

Discovery submitted acceptable financial disclosure statements. None of the disclosures raise questions about financial conflict of interest.

c. Other

There are no outstanding issues with consults received from the Office of Prescription Drug Promotion (OPDP, formerly DDMAC), DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Surfaxin was reviewed during previous cycles by the Division and various groups of the Agency and determined to be acceptable.

b. Physician Labeling

During a previous (third) review cycle the Division performed a thorough review of the product label and made many changes to the original labeling proposed by Discovery including the addition of a (b) (4) the increased risk of death observed when lucinactant was administered to the lungs of adults with ARDS via flexible bronchoscopy. For the current submission, Discovery was required to submit the product label in the PLR format. The Division extensively revised the Warnings and Precautions, Adverse Reactions, and Clinical Studies sections of the PI submitted by the company to better comply with the required PLR format and add context to many of the statements made in the previous version of the label which, at the time it was written, was modeled after the labels of other approved surfactant product labels which remain in the older format. The label was also reviewed by the Office of Medical Policy Programs (OMPP), the Office of Surveillance and Epidemiology (OSE)/DMEPA, and by OPDP.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, ONDQA, OPMP, and DMEPA, and were found to be acceptable.

d. Patient Labeling and Medication Guide

There is a no Patient Counseling Information (Instruction for Use and Patient Package Insert) or Medication Guide and this is acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Discovery has submitted adequate data to support approval of Surfaxin (lucinactant) Intratracheal Suspension for the prevention of RDS in premature infants at high risk of

RDS at a dose of 5.8 mL per kg birth weight for up to 4 doses given every 6 hours within the first 48 hours of life. The recommended regulatory action for this application is approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment of Surfaxin for the prevention of RDS in premature infants at high risk of RDS supports its approval. The efficacy and safety data, as reviewed in section 7 and 8 above, has been demonstrated. Administration of exogenous surfactant products are potentially life-saving treatments for RDS. The development of a validated bioassay ensures the biological activity of the drug product and also supports approval of Surfaxin.

c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

d. Post-marketing Study Commitments

There will be one post-marketing commitment. Based on the conclusions of the GLP/GMP inspections carried out at the facilities involved in testing biological activity of the drug product and in agreement with the NDA amendment dated Mar 1, 2012, the following PMC has been agreed to by the Applicant:

You commit to transfer responsibility from Discovery to (b) (4) (b) (4) for quality assurance 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. Your PAS should include a statement 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 the approval of PA supplemental application by the Agency.

Final Report Submission: January 30, 2014

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/s/

LYDIA I GILBERT MCCLAIN

03/06/2012

Acting Division Director
Entered in DARRTS for Dr Badrul Chowdhury Division Director