CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-521

CORRESPONDENCE

JUL 12 1996

**MEMORANDUM**

DATE: July 12, 1996

TO: NDA 20-521

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products HFD-570

/S/ 7/12/96

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-521 for Infasurf (calf lung surfactant extract, CLSE) was originally submitted by ONY (in partnership with Forest Laboratories) on March 13, 1995. Following extensive internal discussions regarding the issue of Orphan Drug Exclusivity protection for Survanta and the similarity/differences between Infasurf and Survanta, the Division refused the file the application in a letter dated May 10, 1995 based on the fact that Infasurf and Survanta were deemed to be the "same" drug for the purposes of Orphan Drug Exclusivity and there were no data in the original application to demonstrate clinical superiority of Infasurf over Survanta. The Division met with the sponsor on July 6, 1995 to review the reasons for the RTF decision. At that meeting the sponsor presented a scientific argument and some preliminary data which suggested that Infasurf and Survanta were not the "same" drug; the argument was primarily based on the sponsor's assertion that Infasurf contained substantially more surfactant associated protein B (SP-B) than Survanta and that the levels of SP-B in Survanta were so low as to be inactive. Following internal discussions of the new information presented by the sponsor at the meeting of July 6, 1995, the Division notified ONY in a letter dated July 13, 1995 that the application would be refiled provided; 1) the data supporting the contribution of SP-B to the effect of Infasurf was included in the resubmitted NDA, and 2) the sponsor commit to providing

The NDA was resubmitted on July 31, 1995 with the above data/commitments as well as a comparative clinical trial of Infasurf versus Survanta for the prophylaxis and treatment of RDS. The resubmitted application was filed by the Division. An IR letter listing CMC deficiencies was issued on February 28, 1996 and a meeting with the sponsor to discuss the issues contained in this letter was held on March 20, 1996. The sponsor was informed by teleconference on April 26, 1996 and by letter on May 24, 1996 that the Center had determined that Infasurf and Survanta were considered to be the "same" drug for the purposes of Orphan Drug Exclusivity and that Infasurf could not be approved until the 7 year Orphan Drug Exclusivity for Survanta expires in July 1998. The sponsor was also informed that if they should desire to attempt to demonstrate that Infasurf was in fact "different" from Survanta for the purposes of Orphan Drug Exclusivity based on an "active moiety" concept for a particular component of the surfactants that they would be required to "demonstrate both that the particular component is present and active in one surfactant and that it is either not present or present at levels that are inactive in the other surfactant". Another meeting with the sponsor to discuss several of the

CMC issues contained in the February 28, 1996 CMC IR letter was held on July 9, 1996. The current User Fee Goal Date for NDA 20-521 is July 31, 1996.

Clinical

The proposed indication for Infasurf is for "the prevention of Respiratory Distress Syndrome (RDS) in premature infants and the treatment ("rescue") of newborn infants who develop RDS. Infasurf significantly decreases the incidence of RDS, the severity of RDS, mortality due to RDS, and air leaks associated with RDS." In support of this indication, the sponsor submitted three multicenter, randomized, masked, active-controlled, trials of Infasurf versus either Exosurf or Survanta for the prophylaxis or treatment of RDS (Study SCT-P vs Exosurf for prophylaxis of RDS, Study SCT-T vs Exosurf for the treatment of RDS, and ISCT-92 versus Survanta for the prophylaxis and treatment of RDS). Studies SCT-P and SCT-T are considered the pivotal demonstrations of efficacy; Study ISCT-92 is considered supportive. Please see the integrated Clinical/Statistical Review by Drs. Pina and Koutsoukos for more complete details on the design/results of these studies. A brief overview of each of these studies will be presented here.

Efficacy:

Study SCT-P: This trial compared Infasurf (3 ml/kg Q12 hrs for up to 3 doses) and Exosurf (5 ml/kg Q12 hrs for up to 3 doses) for the prevention of RDS in 871 premature babies ≤28 weeks gestation and ≤1100 grams body weight. For the primary endpoints in the intent-to-treat population, Infasurf was statistically significantly more effective than Exosurf in decreasing the incidence of RDS and mortality secondary to RDS and not significantly different (and essentially numerically the same) for the incidence of BPD. For the secondary endpoints in the intent-to-treat population, Infasurf was generally equal to, or numerically better than Exosurf for all endpoints and statistically significantly better than Exosurf for some endpoints (e.g., total respiratory mortality, incidence of crossover surfactant treatment).

Study SCT-T: This study compared Infasurf (3 ml/kg, two doses Q12 hrs) and Exosurf (5 ml/kg, two doses Q12 hrs) for the treatment of RDS in 1,133 premature infants with established RDS. For the primary endpoints in the intent-to-treat population, Infasurf was statistically significantly more effective than Exosurf in reducing the incidence of RDS related air leaks (the original protocol defined primary endpoint) but was not statistically significantly different from Exosurf for the severity of RDS over the first 24 hours, the incidence of BPD, or mortality secondary to RDS (for each of these three "primary" endpoints Infasurf was numerically the same or slightly better than Exosurf). For the secondary endpoints in the intent-to-treat population, Infasurf was numerically better, though not statistically different from Exosurf, on total respiratory mortality, neonatal mortality, incidence of crossover surfactant treatment, incidence of acute pulmonary hemorrhage, and severity of BPD.

Study ISCT-92: This study compared Infasurf (4 ml/kg of 25 mg phospholipids/ml suspension [proposed marketed formulation is 35 mg/ml], up to four doses) and Survanta (4 mg/kg, up to 4 doses) for the prevention of RDS in 463 premature infants ≤30 weeks gestation and ≤1250 grams body weight and for the treatment of RDS in 662 premature infants with established RDS. Prophylaxis: For the intent to treat population (Note: the primary endpoint(s) were not

prospectively identified, retrospectively intact cardiopulmonary survival was defined as the primary endpoint; the power calculations for the study were reported to have been based on detection of a 15% net reduction in the Survanta rate of babies requiring two doses of drug), there was a trend favoring Survanta for intact CP survival at 28 days ($p=0.08$), there were statistically significantly fewer total deaths ($p=0.03$) and respiratory deaths ($p=0.005$) in the Survanta group (no difference in non-respiratory deaths), there was no difference in the incidence of BPD at 28 days, there was no difference in the incidence of RDS or the severity of RDS, and there was no difference in the incidence of pulmonary complications of RDS (i.e., PTX, PIE, any air leak). There were statistically significant differences in the hours between dose 2 to dose 3 and dose 3 to dose 4 in favor of Infasurf (mean difference between groups of 5-7 hours). Treatment: For the intent to treat population (see note above regarding primary endpoint designation, the power calculations for the study were reported to have been based on detection of an 18% net reduction in the Survanta rate of babies requiring three doses of drug), there was no difference in the incidence of intact CP survival at 28 days, there was no difference for any mortality parameter, there was no difference in incidence of BPD at 28 days, there were statistically significant differences in RDS severity at 24 hours in favor of Infasurf, and there was no difference in pulmonary complications of RDS. As observed in the prophylaxis trial, there were statistically significant differences in the hours between dose 1 to dose 2, dose 2 to dose 3, and dose 3 to dose 4 in favor of Infasurf (mean difference between groups of 3-4 hours). In addition, statistically significantly fewer babies in the Infasurf group required 4 or more doses of drug compared to Survanta. The were also small, but statistically significant differences in the level of $FiO_2$ support and mean airway pressure (MAP) in favor of Infasurf during the first 48 hours of treatment. Overall, the results of the prophylaxis and treatment components of this trial do not clearly demonstrate that Infasurf is clinically superior to Exosurf with regard to efficacy outcomes. While Infasurf did have a longer dosing interval than Survanta in both arms of the trial and significantly reduced the number of babies requiring 4 or more doses as well as $FiO_2$ and MAP in the treatment arm, these differences were small and of questionable clinical significance given the lack of correction of these results for multiple statistical comparisons and the observed statistically significant decreased mortality in the Survanta arm of the prophylaxis trial. At best, this trial is supportive of the efficacy of Infasurf in the prophylaxis and treatment of RDS given the fact that for many of the endpoints for which Survanta has been demonstrated in placebo controlled trials to be effective Infasurf was numerically similar to Survanta.

Safety:

Study SCT-P: For the intent to treat population, there was a statistically significant greater incidence of periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) in the Infasurf group when analyzed as the combination of PVL and IVH or when analyzed as PVL or IVH or both. When analyzed based on patient outcome (i.e., 'died or survived with PVL and/or severe IVH' or 'survived without PVL or severe IVH) there were no statistically significant differences between the treatment groups, however, very small numerical trends favored a better outcome with Exosurf. For complications of prematurity (e.g., retinopathy of prematurity, patent ductus arteriosis, apnea, necrotizing entercolitis, sepsis) no differences were observed between the treatment groups. There were also statistically significant greater incidences of adverse events associated with the administration of the study drug (bradycardia,

airway obstruction, cyanosis, manual ventilation) in the Infasurf group.

Study SCT-T: For the intent to treat population, there was a statistically significant lesser incidence of IVH in the Infasurf group, however, when analyzed as the incidence of PVL and IVH there was a statistically significant greater incidence in the Infasurf group. When analyzed based on patient outcome (see above) no differences were seen between the treatment groups. For complications of prematurity, no differences were observed between the treatment groups. As in the Exosurf prophylaxis trial, there were statistically significant greater incidences of adverse events associated with the administration of the study drug (bradycardia, airway obstruction, cyanosis, manual ventilation) in the Infasurf group.

ISCT-92: Prophylaxis No statistically significant differences were observed for PVL, IVH, and other complications of prematurity, however, with regard to PVL and IVH there were small numerical trends in favor of lower incidence and better patient outcomes with Survanta. There were statistically significant greater incidences of adverse events associated with the administration of study drug (airway obstruction, requirement for suctioning within one hour of dosing) in the Infasurf group. Treatment There was a statistically significant greater incidence of mild IVH in the Survanta group and numerically more patients with severe IVH in the Infasurf arm. As in each of the other studies, there were statistically significant greater incidences (or strong trends) of adverse events associated with the administration of the study drug (airway obstruction, requirement for suctioning within one hour $p=0.07$).

Summary:

The two pivotal trials which compared Infasurf to Exosurf adequately support the efficacy of Infasurf for the prevention and treatment of RDS in premature infants. The trial which compared Infasurf to Survanta failed to demonstrate that Infasurf is clinically superior to Survanta; the findings of an increased dosing interval and decreased $FiO_2$ and MAP in the Infasurf group were of questionable clinical significance and insufficient to explain away the statistically significant decreased mortality in the Survanta treated group in the prophylaxis trial. From a safety perspective, the major concerns are the apparent increased incidence of intraventricular hemorrhage and adverse events associated with administration of the drug seen in the Infasurf group when compared to both Exosurf and Survanta. It is uncertain how this finding may be linked to the use of Infasurf and when the data are analyzed on the basis of patient outcome no statistically significant differences were seen. The clinical significance of these findings, therefore, remain unclear and should not preclude approval of Infasurf with appropriate labeling. The adverse events associated with administration of the drug were clearly more frequent with Infasurf than Exosurf (although Infasurf was more effective) and somewhat more frequent than with Survanta. These adverse events were generally transient and not severe and should not preclude the approval of Infasurf with appropriate labeling for adverse events and administration precautions.

Infasurf is considered clinically approvable for the prevention and treatment of RDS in premature infants with appropriate labeling to detail the findings of the pivotal clinical trials summarized above.

Preclinical

Please see the preclinical review by Dr. Choi for a more detailed assessment of the preclinical studies submitted by the sponsor. With regard to toxicology, the sponsor submitted an acute intratracheal toxicity study in newborn rabbits and a 7 day intratracheal toxicity study in newborn pigs. There was little toxicity of Infasurf in these studies with the exception of clinical findings associated with the actual administration of the drug. Infasurf was not mutagenic in the Ames test. No carcinogenicity or chronic toxicology studies were conducted, or required, for this application due to the limited duration of dosing proposed for labeling. The sponsor only submitted one multi-dose toxicology study to the NDA which does not meet the usual requirement of two species. This issue was dealt with by the Division in the past and the decision was made to not require the second species given the extensive clinical data available for the product.

Infasurf is considered approvable from a preclinical standpoint with appropriate labeling to reflect the available preclinical database.

CMC

Please see the CMC review by Dr. Nashed for more complete details of the CMC review of Infasurf.

As noted in the Administrative section of this memo, the sponsor has been informed that the Center has determined that naturally derived surfactants are the "same" drug for the purposes of Orphan Drug Exclusivity. In the meeting of July 6, 1996 the sponsor argued that Infasurf is not the "same" drug as Survanta and primarily based on their argument on their contention that the levels of SP-B in Infasurf are much higher than those in Survanta and that the SP-B levels in Infasurf are critical to its activity while the levels of SP-B in Survanta are not active. The sponsor was requested to submit data and methods for assay of SP-B in Infasurf and Survanta and informed that a regulatory specification would be required for this claimed active ingredient. Subsequently, in the letter dated May 24, 1996, the sponsor was informed that if they choose to challenge the Agency's determination that Infasurf and Survanta are the "same" drug based on the "active moiety" concept that they would need to "demonstrate both that the particular component is present and active in one surfactant and that it is either not present or present at levels that are inactive in the other surfactant". The sponsor has submitted data and methods for the assay of SP-B in Infasurf and Survanta and this has been reviewed by Dr. Nashed (see CMC deficiencies in the action letter).

Infasurf is considered not-approvable from a CMC standpoint and the outstanding deficiencies will be included in the action letter to the sponsor.

Biopharmaceutics

The sponsor requested a waiver of the requirement for submitting evidence of in-vivo bioavailability (21 CFR 320.22(e)) of Infasurf and Dr. Gillespie has recommended that that request be granted.

Infasurf is considered approvable from a biopharmaceutics standpoint and a waiver of the requirement for submitting evidence of in-vivo bioavailability should be granted.

Data Verification

The Division of Scientific Investigations (DSI) completed audits at a total of 6 clinical sites from the pivotal efficacy trials (SCT-P, SCT-T). Five of the sites were reported as VAI and one site was reported as NAI. The audit reports were reviewed by Dr. Pina who noted that at 3 of the 6 sites patients were reported by the investigator to have air leaks on their CXR, however, these findings were not reported by the sponsor in the NDA. This finding is particularly important (despite the fact that based on the data Dr. Pina reviewed it appears that the failure to report the air leaks resulted in Infasurf actually looking worse on this endpoint) since the incidence of air leaks was the primary endpoint for SCT-T and an important secondary endpoint in SCT-P. These findings bring into question the integrity of the NDA database and the sponsor will be asked in the action letter to explain how these discrepancies occurred and to provide a detailed report of the auditing procedures that were conducted by the sponsor in putting together the NDA to insure that this is not a systematic problem.

Labeling

The proposed trade name, Infasurf, is acceptable to the Division and was reviewed and found

acceptable by the Labeling and Nomenclature Committee. The remainder of the labeling has not been reviewed at this point since the NDA is not being approved at this point and the outstanding deficiencies and Orphan Drug Exclusivity issues will preclude approval in the near future. A comment will be added to the action letter that labeling comments will be provided once the application is closer to being approved.

Microbiology

Per the review by Dr. Vincent the sponsor has submitted adequate data to assure sterility of the drug product provided the sponsor commit to additional controls which will be communicated to the sponsor in the action letter.

Conclusion

The primary outstanding issues for this NDA are the CMC deficiencies and the issue of the findings from the DSI audit and the question of the overall integrity of the database. From a clinical standpoint the sponsor has provided adequate data to support the safety and efficacy of Infasurf (assuming the integrity of the database is assured), therefore, in accord with current Center policy on the issuance of action letters, this application is APPROVABLE. Deficiencies from the various disciplines will be communicated to the sponsor in the action letter.

cc:
NDA 20-521
HFD-570 Division Files
HFD-570/Jenkins
HFD-570/Schumaker
HFD-570/Kuzmik
HFD-570/Himmel
HFD-570/Pina

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-521

JUL 25 1996

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your July 27, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract) Intratracheal Suspension.

We acknowledge receipt of your submissions dated March 13, June 30, August 4, 10, 21 and 22, September 21 and 26, October 16, November 3, 6, and 8, and December 1, 4, and 15, 1995, and January 23, February 8 and 20, March 6, April 12, May 10 and 24, and July 11, 1996.

Reference is made to our February 28 and May 24, 1996, letters, your July 3, 1996, telephone conversation with Ms. Carol Vincent, microbiology reviewer, and our July 9, 1996, meeting.

We have completed the review of this application as submitted with draft labeling and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information.

# THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

6 pages

Since calf lung surfactant extract (CLSE) is not an established name as described under 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, you should apply to the United States Adopted Names (USAN) Council for adoption of a name that will comply with that section of the Act. They can be contacted at the following address:

U.S. Adopted Names Council
American Medical Association
P.O. Box 10970
Chicago, IL 60610

We remind you that satisfactory inspections of all facilities involved in the manufacturing and testing of Infasurf for conformance with current good manufacturing practices (cGMP) are required before this application may be approved.

We are reserving comment on the proposed label and labeling until the application is found adequate in other respects.

As you know, due to the orphan exclusivity granted to Ross Laboratories' product Survanta, this application may not be approved until July 1, 1998, unless, as discussed in our letter of May 24, 1996, you can show to our satisfaction that Infasurf and Survanta should not be considered to be "the same drug."

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. 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 may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact Ms. Betty Kuzmik, Project Manager, at (301)827-1051.

Sincerely,

/S/

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

July 15, 1997

Edmund A. Egan, MD
President
ONY, Inc.
1576 Sweet Home Road
Amherst, NY 14228

Dear Dr. Egan:

This correspondence responds to your letter of March 14, 1997, submitted under the dispute resolution provisions of 21 CFR 314.103. In that letter you requested resolution of whether Infasurf is the "same" drug as Survanta within the meaning of the Orphan Drug Act (ODA) exclusivity regulations found at 21 CFR 316.3(b)(13).

Since our receipt of that letter, several communications have occurred between you and the Center for Drug Evaluation and Research (CDER), which have also been considered in preparing this response:

May 7, 1997: Tentative approval letter to NDA 20-521 (Infasurf)
May 13, 1997: Your letter to Dr. Bilstad, Director, Office of Drug Evaluation II
May 28, 1997: Your FAX to the Division of Pulmonary Drug Products providing preliminary results of a study designed to demonstrate that Infasurf is not the "same" drug as Survanta
June 9, 1997: Your letter to Mr. Morrison, CDER Ombudsman
June 11, 1997: Presentation (transcribed) by you, your consultants and attorneys to Drs. Woodcock, Lumpkin and FDA staff members

We have carefully reviewed these materials and have conducted internal meetings with appropriate agency staff to deliberate the issues you raised. For the reasons outlined briefly below, we have concluded that, in the context of the ODA and its corresponding regulations, Infasurf and Survanta are the "same" drug, and Infasurf has not been shown to be clinically superior to Survanta or to make a major contribution to patient care as defined in the regulations. Hence, we affirm the tentative nature of the approval of NDA 20-521, which precludes marketing until July 1, 1998, when the ODA exclusivity granted to Survanta expires.

Although we have concluded that you have not demonstrated that Infasurf is clinically superior to Survanta or that it makes a major contribution to patient care not currently provided by Survanta, we understand and are sympathetic to your concern that there may be a population of neonatal patients with Respiratory Distress Syndrome (RDS) who fail to respond to Survanta but who may respond to Infasurf.

The Federal Food, Drug and Cosmetic Act permits great flexibility in the conditions under which new drugs are studied. We believe that your assertion that Infasurf is clinically superior to Survanta in unresponsive neonates, although currently not supported by clinical data, should be pursued and that the efficacy of Infasurf for patients who fail Survanta ought to be explored. The Center stands ready to work with you to expeditiously devise an appropriate mechanism to study Infasurf in clinical settings that may conclusively answer the questions regarding its effectiveness relative to Survanta. We strongly encourage you to contact the Division of Pulmonary Drug Products to discuss the design of such a study pending full marketing of Infasurf next year.

Our conclusions regarding the specific arguments made in your appeal have been grouped into the following general areas:

Composition and Activity Differences Between Infasurf and Survanta:

The agency's decision in 1991 that approval of Survanta was not blocked by Exosurf's orphan drug exclusivity does not compel the same conclusion with respect to Infasurf and Survanta. Exosurf is a mixture of three synthetic active ingredients, with no undefined components. Two of the three active components in Exosurf (cetyl alcohol and tyloxapol) are not present in Survanta. In contrast, Survanta is a complex mixture of lipids and proteins derived from bovine lungs. Exosurf and Survanta differ markedly in composition and have only one component in common (DPPC).

On the other hand, both Infasurf and Survanta are complex mixtures of lipids and proteins derived from bovine lungs. They are very similar in their composition, with both products containing all six of the "active" components (DPPC, PC, SP-B, SP-C, that were identified in your presentation of June 11 in addition to a number of other identified components that may contribute to their activity. Although Infasurf and Survanta contain differing quantities of these six components, they are both effective surfactants, and you have not demonstrated that such quantitative differences are relevant to the clinical activity of the products. Individual components of Survanta may be important to its overall activity, but it is difficult to ascertain accurately the relative contribution of each one. Thus, in the absence of more data, all components must be considered to contribute to the activity of these products.

Further, we do not agree with your assertion, based on the statements contained in the description section of the Survanta package insert, that Survanta could contain no protein at all, in contrast to Infasurf, which contains specified amounts of total protein and SP-B. Based upon our knowledge of the Survanta NDA, we are

confident that all batches of Survanta released for marketing do contain protein. Further, data from your own laboratories have consistently demonstrated that marketed batches of Survanta contain protein and SP-B.

Clinical Superiority of Infasurf over Survanta:

We have conducted a thorough review of the Infasurf versus Survanta comparative trial in your NDA and have concluded that the data do not support a claim of clinical superiority for Infasurf. Infasurf's superiority over Survanta was not demonstrated for any of the recognized clinically relevant endpoints (e.g., mortality, incidence of RDS, incidence of bronchopulmonary dysplasia, air leaks, etc.). In fact, in the prophylaxis arm of the trial mortality was actually lower for neonates treated with Survanta than those treated with Infasurf. The small differences observed between the products in physiologic endpoints, such as $FiO_2$ and MAP, are of unknown clinical significance and are not adequate to support a claim of clinical superiority. Likewise, your post hoc subset analysis of patients with "severe, persistent RDS," while raising a hypothesis for future study, cannot be the basis of a finding of clinical superiority. Further, the small differences observed between Infasurf and Survanta in frequency of dosing, percent of patients requiring a full course of treatment, and the like are not an adequate basis to support a finding that Infasurf provides a major contribution to patient care not currently provided by Survanta.

We also disagree with your assertion that the "Acute Clinical Effects" paragraph in the Clinical Pharmacology section of the Infasurf labeling suggests clinical superiority. The cited paragraph describes the acute clinical effects observed in infants following treatment with Infasurf compared to baseline, not a comparison of Infasurf-treated versus Survanta-treated infants. Similar language is found in Survanta and Exosurf labeling as well.

Interpretation of the Orphan Drug Exclusivity Regulations:

We agree that the orphan drug regulations do not identify a specific regulatory mechanism for determining "sameness" in the case of Infasurf and Survanta, drugs consisting of mixtures of large and small molecules. However, we believe that the relationship between Infasurf and Survanta is analogous to that described in 21 CFR 316.3(b)(13)(ii)(D). Infasurf and Survanta are closely related drug products (lung surfactants derived from bovine sources). Also, they are complex (composed of many components), partly definable (not all of the constituent molecules have been identified and quantified), and have the same therapeutic intent. Therefore, we believe Infasurf and Survanta should be considered the same from the chemical standpoint in the context of orphan drug exclusivity.

As you can appreciate, this discussion of our conclusions is not exhaustive, given the quantity of written materials and oral arguments you have provided and given our extensive review, analysis and internal discussions. However, we have enclosed a more detailed analysis prepared by the Division of Pulmonary Drug Products that was relied upon by CDER, along with other materials, in considering your appeal. We hope you find it helpful to you in understanding the basis for our decision.

In closing, we would like to express our sincere appreciation for your patience and for your professionalism while pursuing this appeal. We look forward to working with you in a continuing cooperative effort in this critical health area.

Sincerely yours,

/S/

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research

Enclosure:
Memorandum dated 7/2/97 Jenkins to Woodcock, redacted for FOIA

APPEARS THIS WAY
ON ORIGINAL

NDA 20-521

SEP 26 1996

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your July 27, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract) Intratracheal Suspension.

Reference is also made to the Agency's letter dated May 24, 1996, and your submissions dated July 19 and August 13, 1996, in which you propose a plan to demonstrate that Infasurf and Survanta are not the "same drug" under Orphan Drug Regulations.

We agree with your proposal to demonstrate that Infasurf and Survanta differ in a specific active component by demonstrating both that the particular component is present and active in one surfactant and that it is either not present or present at levels that render it inactive in the other surfactant. However, we have the following comments regarding your proposal.

1. All experimental procedures and tests should be carried out in replicate on both drug products, Survanta and Infasurf, under the same experimental conditions to assure consistency and validity. Your August 13, 1996, proposal to perform experimental tests on Infasurf only, is unacceptable.

2. All methods should be properly described and validated. The choice of methods should be adequately justified to assure sufficient characterization and quantitative composition of the "modified" drug product.

3. The methods used for assessment of *in vitro* activity of the drug product preparations should include both the and test. If alternative methods will be used, they must be shown to be well correlated with clinical effects.

4. All tests and measurements should be conducted in a randomized and fully blinded fashion.

5. A detailed protocol of your experimental plan and your plan for analysis of the data should be submitted for review prior to the initiation of the experimental studies. The protocol should include a prespecified definition, rationale and *in vivo* data-based justification of what will be considered a meaningful difference, or lack thereof, between formulations.

Should you have any questions, please contact Ms. Betty Kuzmik, Project Manager, at (301)827-1051.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-521

MAY 24 1996

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York, 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your pending July 27, 1995 new drug application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf.

Reference is also made to the April 26, 1996 telephone conference between Dr. Larry Olanoff, Mr. Laszlo Ek, Mr. Sultan Aziz, Ms. Debbie Urquhart from Forest Laboratories, Mr. Alan Kaplan from his Washington, D.C. law office, Mr. William Ferguson and yourself from ONY, Inc., and Dr. James Bilstad from the Office of Drug Evalution II, Dr. John Jenkins, Dr. Jean Nashed, and Ms. Betty Kuzmik from this Division.

At that telephone conference, we informed you that the Agency has determined, based on the information currently available, that Infasurf and Survanta are considered the same drug from the standpoint of the Orphan Drug Regulations. The rationale supporting this decision is that, in contrast to drugs composed of small molecules to which the concept of an active moiety (21 CFR 316.3(b)(2)) applies, surfactants are a complex mixture of both large and small molecules, many of which have poorly defined specific or unique physiologic functions. As such, surfactants are most like the macromolecules in that it would be trivially easy to make minor changes in a surfactant that would leave the activity of the drug unaltered, but would create a "new drug" if the micromolecular definition of active moiety were applied. The Agency believes that the paradigm of macromolecules should be applied to surfactant drugs. 21 CFR 316.3(b)(13)(ii)(D), states that "Closely related, complex partly definable drugs with similar therapeutic intent,...would be considered the same unless the subsequent drug was shown to be clinically superior." Therefore, based on currently available data, we conclude that Infasurf and Survanta should be considered the "same drug."

As we discussed, should you wish to apply the "active moiety" concept to a particular component of surfactants, you would need to demonstrate both that the particular component is present and active in one surfactant and that it is either not present or present at levels that are inactive in the other surfactant. As discussed in the Federal Register of December 29, 1992 (57 FR 62077), different in vitro biologic activity will not normally suffice to support a claim of clinical superiority because of concern that in vitro activity may not correlate with clinical effects. As such, any in vitro or pre-clinical models used to support the activity of individual components of surfactants should be well correlated with clinical effects.

Sincerely,

/S/

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug evaluation II
Center for Drug Evaluation and Research

cc:
NDA 20-521
HFD-570/Div File
HFD-570/Pina
HFD-570/Himmel
HFD-570/Nashed
HFD-570/Poochikian
HFD-570/Koutsoukos
HFD-570/Wilson
HFD-570/Choi
HFD-570/Sun
HFD-570/Gillespie
HFD-570/Conner
HFD-570/Schumaker/5-21-96
HF-35/Mccormick
GCF-1/Dickinson
R/D by MHimmel
Draft letter typed by Bkuzmik/5-14-96 and 5-21-96
Reviewed by Drs. McCormick, Jenkins, Bilstad, and Ms. Dickinson/5-21-96

/S/ 5/22/96

/S/ 5/24/96

/S/ 5/23/96

KUZMIK

NDA 20-521

FEB 28 1996

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your pending July 27, 1995 new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf.

We also refer to your amendments dated August 10, 22, September 26, and December 1, 1995.

To complete our review of the chemistry sections of your submission, we request the following.

# THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Betty Kuzmik
Project Manager
(301) 827-1054

Sincerely yours,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachments A and B enclosed

cc:

Original NDA 20-521 —
HFD-570/Div. Files
HFD-570/CSO/Betty Kuzmik
HFD-570/JNashed
HFD-570/Pina
HFD-570/Choi
HFD-570/Gillespie
HFD-570/Koutsoukos

DISTRICT OFFICE

/S/ 2/27/96

/S/ 2/27/96

/S/ 2/27/96

drafted: BK/February 21, 1996/n20521.chm
reviewed by: Cschumaker/2-21-96; Jnashed/2-23-96; Gpoochikian/2-23-96; Mpina/2-22-96; MHimmel/2-23-96
final: SmithV 2/26/96

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

Kuzmik

NDA 20-521

AUG 8 1995

Ony, Inc.
c/o Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022-4731

Attention: Michael M. Rosen, Ph.D.
Director of Regulatory Affairs

Dear Dr. Rosen:

We have received your new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Infasurf (calf lung surfactant extract) Intratracheal Suspension

Therapeutic Classification: Standard

Date of Resubmitted Application: July 27, 1995

Date of Receipt: July 31, 1995

Our Reference Number: NDA 20-521

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 29, 1995 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Betty Kuzmik
Consumer Safety Officer
Telephone: (301) 827-1054

APPEARS THIS WAY
ON ORIGINAL

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-521
HFD-155/Div. Files
HFD-80
HFD-155/CSO/Betty Kuzmik
HFD-155/Schumaker/8-2-95

/S/ 8/4/95 /S/ 8/4/95

drafted: BKuzmik/August 2, 1995/n20521.ack
Final: Vsmith 8/3/95

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

ONY INC
BAIRD RESEARCH PARK
1576 SWEET HOME ROAD • AMHERST, NEW YORK 14228
(716) 636-9096 (800) 274-4669



ORIGINAL

July 27, 1995



John Jenkins, MD, Acting Director
Division of Pulmonary Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-155
5600 Fishers Lane
Rockville, MD 20857

~~N(BC)~~
N(RS)
ORIG AMENDMENT

**Re:** **NDA 20-521 Resubmission**
**Product:** **Infasurf (calf lung surfactant extract)**

Dear Dr. Jenkins,

This is a resubmission of NDA 20-521. Reference is made to your letter dated July 13, 1995 in response to the July 6, 1995 meeting between ONY, Inc, Forest Laboratories and FDA.

In response to item # 1 of that letter we are submitting the data presented at the meeting which supports the contribution of SP-B to the effect of Infasurf. In order to conform with the instructions that the data be submitted "...in a manner consistent with an NDA submission" we have prepared this information as an extension of:

**Section 3.3.1**
**Description of the Physical and Chemical Characteristics of the Drug Substance**

The data contains a substantial amount of data about the drug product and pharmacologic and physiologic activity. However, it was decided to add it into this section of the NDA because its focus is the chemical definition of the Active Moiety of Infasurf and the other surfactants.

The additional text pages have been numbered 03 0004 A through 03 0004 J and 03 0006 A. The additional references have been numbered 03 0105 (A-1) through 03 0105 (A-46). This resubmission data can be stored separately or it can be added to NDA 20-521 without affecting the pagination of the remainder of the NDA document.

We will provide comparative CMC data from an FDA inspected laboratory for the comparative analysis of SP-B using appropriately validated methods in 4-6 lots of Infasurf and Survanta by December 1, 1995. We will include the dates of testing, the batch number and the expiration date for each analysis.

In addition we will develop specifications of components of Infasurf including SP-B. Using retained vials from lots used for clinical trials we will link SP-B concentration in clinical trial lots to that in to-be-market lots. This development will proceed in parallel with the comparative testing of SP-B between Infasurf and Survanta.

Sincerely,

FOREST LABORATORIES, INC

Michael M. Rosen, PhD for
Director of Regulatory Affairs

ONY, INC.

Edmund A. Egan, MD
President

KUZMIK

NDA 20-521

JUL 13 1995

ONY, Inc.
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Reference is made to your March 13, 1995 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract).

Further reference is made to our refuse to file (RTF) letter dated May 10, 1995, your May 18, 1995 request for a meeting to discuss the RTF letter and the July 6, 1995 meeting that took place between representatives of ONY, Inc. and FDA.

The new information that was presented at the meeting provides a theoretically valid argument that Infasurf is different from Survanta. We are willing to file your NDA if the following are included in your resubmission.

1. The data which were presented at the meeting and which support the contribution of SPB to the effect of Infasurf must be submitted in a manner consistent with an NDA submission.

2. Commit to provide comparative CMC data from an FDA inspected laboratory for the analysis of the SPB in Survanta and Infasurf by no later than 4 months after the NDA is resubmitted. Appropriately validated methods should be used to generate the requested comparative data on 4 to 6 batches of each product. The data should include the batch number and expiration of the batch tested and the date the analysis was performed.

If the determination is made that Infasurf is different from Survanta based on the above comparative data, appropriate regulatory specifications must be set for various components in Infasurf including SPB. Since SPB was not specifically assayed in the clinical lots, you must propose a plan for linking the clinical lots with the to-be-marketed lots with regard to concentration of SPB.

The application will be considered resubmitted when we have received the data requested in #1. above.

If you have any questions, please call Ms. Betty Kuzmik, Consumer Safety Officer at (301)827-1054.

Sincerely yours,

John K. Jenkins, M.D.
Acting Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig NDA 20-521
HFD-155/Div File
HFD-155/Himmel
HFD-155/Pina
HFD-155/Poochikian
HFD-155/Ng
HFD-155/Kuzmik
R/D/Schumaker/7-10-95
Revised:MHimmel/7-10-95
GPoochikian/7-11-95
LNg/7-11-95
R/D init:MPina/7-11-95
c:\schumake\n20521.let
F/T by: VSmith
GENERAL CORRESPONDENCE

/S/ 7/13/95

/S/ 7/13/95

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the General Counsel

Office of the Chief Counsel
Food and Drug Administration
5600 Fishers Lane, GCF-1
Rockville, MD 20857

# MEMORANDUM

**Date:** May 28, 1996

**To:** Dr. James M. Bilstad, HFD-102

**From:** Elizabeth Dickinson, GCF-1 EHD

**Subject:** Refusal to File/Orphan Exclusivity

You have asked whether the agency may refuse to file an NDA when the approval of the application will be blocked by another sponsor's exclusivity for the same drug product under the Orphan Drug provisions of the Federal Food, Drug, and Cosmetic Act.

For the reasons given below, I believe that the agency may not refuse to file an application under these circumstances.

The Orphan Drug provisions of the FFDCA provide for a grant of seven years of market exclusivity for drug products that are approved for the treatment of diseases or conditions affecting fewer than 200,000 persons in the U.S. During this period of exclusivity, FDA may not approve any other application for the same drug for the same indication. The preamble to the final regulations implementing the exclusivity portions of the Orphan Drug Act states that

> once the agency determines that approval of a drug would be temporarily barred by the exclusive marketing provisions of the Orphan Drug Act, the timing of the review will be decided on a case-by-case basis by the appropriate division... . Such decisions will be based on time and resource considerations as well as on the complexity of information to be considered.

57 Fed. Reg. 62076-77 (December 29, 1992).

Although this language apparently was intended to give the agency some flexibility in deciding when to review applications for drug products that could not be approved immediately due to orphan exclusivity, there is no corresponding provision in the regulations that provides a legal basis for refusing to file an application under these circumstances.

APPEARS THIS WAY
ON ORIGINAL

The Orphan Drug regulations address, among other issues, the requirements for orphan drug designation, the basis for determining whether two drug products are "the same," and the granting of Orphan Drug exclusivity. See generally 21 C.F.R. § 316. The filing of an NDA for a drug product that has obtained an orphan product designation under §316.24 is governed by the general NDA filing regulations at 21 C.F.R § 314.101; there are no filing regulations specific to orphan-designated products.

The filing regulations provide that the agency "will file" an NDA if it finds that none of the reasons in § 314.101(d) or (e) apply. None of the enumerated reasons is applicable to an NDA that could not be approved because of orphan exclusivity. Moreover, there is no general "catch-all" provision that could provide a basis for refusing to file the application under the circumstances contemplated by the preamble language. Absent such specific or general provision in the regulations, the agency may not refuse to file an NDA on the grounds that approval of the application would be barred by another sponsor's orphan exclusivity.

cc: Dr. Robert Temple, HFD-101
Linda Carter, HFD-101
Dr. John J. McCormick, ODP
Peter Vaccari, OPD

Ann Wion, GCF-1

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-521

JAN 13 1997

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your July 27, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract) Intratracheal Suspension.

Reference is also made to the Agency's letters dated May 24 and September 26, 1996, and your submissions dated July 19, August 13, November 14, and December 24, 1996, in which you propose a plan to demonstrate that Infasurf and Survanta are not the "same drug" under Orphan Drug Regulations.

We have reviewed your November 14, 1996, version of the protocol for testing to prove that Infasurf is different from Survanta and we have found it still inadequate. It should be expanded and modified to provide an adequate amount of details about the proposed testing. The following are general comments and recommendations.

1. The same testing methods, procedures, and conditions should be applied to all Infasurf and Survanta preparations during all drug product modifications, testing, interpretation of the results, etc. Please refer to Protocol 2, (A) and (B) and to comment #1 in our letter dated September 26, 1996.

APPEARS THIS WAY
ON ORIGINAL

2. A detailed analysis of components of Infasurf and Survanta should be provided before and after each modification to assure that only the targeted component has been altered and that the relative proportion of the remaining components and other parameters/attributes of the drug product formulations have not been changed, as discussed during our meetings of March 20 and July 9, 1996. Also, please refer to comment #2 in our September 26, 1996, letter.

3. We recommend that the level of each "depleted" component (see p.3, Methodology A.5) be lowered significantly (at least 10 fold below the usual entry level) and the reconstitution with the "depleted" component be based on the original amount of that ingredient. Furthermore, we advise that the determination of the "activity" of each altered formulation be also supported by the initial testing study of a reasonable number of Survanta and Infasurf batches to establish base line of a given component.

4. We recommend that all drug product preparations, before and after modifications, be tested by the following:

   a. (we recommend reporting value of surface tension with time, e.g., from 0 to 15 min); and

   b.

   A clear and comprehensive plan of data analysis, including assessment of the "activity" of each preparation that is based on the results of both tests should be provided. Please refer to comment #5 below and to comments #3 and #5 in our September 26, 1996, letter.

5. We recommend that the assessment of the "active" and "inactive" status of the Survanta and Infasurf preparations be contingent on the *in vivo* data-based justification of what is considered a meaningful difference. Please refer to comment #5 in our September 26, 1996, letter.

6. The protocol should specify the number of lots of each drug product to be tested, the number of preparations of each altered drug product to be examined, the number of assays to be repeated, etc. All results should be reported in addition to the "mean ± STD" values.

7. Sample sizes should be clearly stated and should be based on a two-sided $\alpha$-level of 0.05 and 80% power.

8. While showing that the two compounds are statistically different, the methodology of testing the null hypothesis of "no difference" will suffice; however, while showing that the two compounds are equivalent, you should state what you mean by equivalence quantitatively as an interval. Hence, the statistical method will be similar to the analysis of a bio-equivalence study. The reference for this methodology is Schuirmann, Donald; "A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability"; Journal of Pharmacometrics and Biopharmaceutics, Vol. 15, No. 6, 1987.

9. Please state prospectively how you plan to combine the p-values obtained from the test and the test.

10. As discussed during the telephone conference of December 9, 1996, your response to the approvable letter of July 25, 1996, is currently under review. An action letter based on our review of your submission will be sent to you within 6 months of the receipt of your submission.

11. The Division continues to believe that the data submitted in this NDA to date are inadequate to demonstrate the clinical superiority of Infasurf over Survanta. However, the Division is committed to working closely with sponsors to facilitate the drug approval process and, as we have in the past, are available to meet with you to discuss your concerns or questions regarding the Infasurf vs Survanta issue.

Should you have any questions or wish to schedule a meeting to discuss our comments on your protocol or to further discuss your contention that Infasurf is clinically superior to Survanta, please contact Ms. Betty Kuzmik, Project Manager, at (301)827-1051.

Sincerely,

/S/

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ONY INC
BAIRD RESEARCH PARK
1576 SWEET HOME ROAD • AMHERST, NEW YORK 14228
(716) 636-9096 (800) 274-4669

May 13, 1997

James Bilstad, MD
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857


Re: NDA 20-521
Infasurf (calfactant)

Dear Dr. Bilstad:

Please refer to your May 7, 1997 letter in which you state that the review of this new drug application has been completed and that it has been concluded by the FDA that the drug is safe and effective for use as recommended in the draft physician labeling and carton and container labeling dated May 5, 1997 and May 6, 1997. Your letter requested, but did not require, specified "minor editorial changes" which you incorporated in the labeling enclosed with your May 7 letter. We are agreeable to making the changes requested.

Your letter indicates that final approval of the new drug application may not issue until July 1, 1998 "due to the orphan exclusivity granted to Ross Laboratories' product Survanta...unless you [ONY] can show that Infasurf and Survanta should not be considered the 'same drug' within the meaning of the Orphan Drug regulations, 21C.F.R. Part 316".

As you and other officials of the Agency know, ONY has taken the consistent position since NDA 20-521 was submitted that Infasurf and Survanta are not "the same drug". The "same drug" question had not been raised by FDA before that time. Since then, ONY has presented data from qualified experts of why the two are not the "same drug". The Agency has never explicitly addressed ONY's data and has never come forward with information to refute it.

As you know too, by letter dated March 14, 1997, ONY requested that FDA convene a panel of independent experts qualified to assess these two drugs, obtain the views of all interested persons, and draw a conclusion as to their same or different status. We requested that the action be completed by mid-April. We have never had a response to the March 14 letter.

While it may appear ironic, it now appears that the "same drug-different drug" question has been resolved by the contents of the FDA-revised physician labeling enclosed with your letter of May 7, 1997. The labeling itself show that Survanta and Infasurf are not "the same drug".

The first indicia is that FDA has determined that the proteins SP-B and SP-C have not been shown to be active components in Survanta but are active components of Infasurf. In its May 26, 1996 letter to ONY, the Agency declared that Infasurf was a macromolecular drug for Orphan Drug purposes under 21 C.F.R. §316.3(b)(13) because its macromolecules, proteins SP-B and SP-C, are active components. Previously, in its review of the Survanta NDA, the Agency decided that the study Abbott Laboratories submitted had not demonstrated that the proteins in Survanta were active. (Chemists Review #4, February 24, 1991 Remark #20, page 5; Review Notes (ii) to (v), page 24-26). The description of the proteins in the package inserts of Survanta and Infasurf reflect the different determinations of protein activity:

(a) Survanta has no specified amount of total protein or of SP-B, only a maximum allowable total protein, <1.0 mg/mL, which means it could have none;

(b) Infasurf has a specified amount of total protein, 0.65 mg/mL, and of SP-B, 0.26 mg/mL.

Since the Agency has not determined that protein(s) in Survanta are active, it cannot be classified as a macromolecular drug under orphan drug regulations because it is not :... a drug composed of large molecules ..." (21 C.F.R. §316.3(b)(13)(ii).) In contrast, Infasurf is a drug composed of active macromolecules by Agency determination. Therefore, ONY is immediately entitled to final approval of Infasurf under the Orphan Drug rules as applied by the Agency to the two drugs.

The second area of distinction that is apparent in the labeling of Infasurf and Survanta are the established names that have been chosen for each drug by USAN and accepted by the FDA. (See 21 U.S.C. §352(e)(1) and 21 C.F.R. §299.4.) The USAN name for Survanta is "beractant." The USAN name for Infasurf is "calfactant." If the products constituted "the same drug," they would have the same established name, in much the same manner as ANDAs carry the same established name as the reference drug upon which they rely for eligibility for approval. By reason of having different established names, Infasurf and Survanta have been officially recognized as different entities, scientifically and legally, and cannot be the same drug.

The third element in the labeling that reveals that Infasurf and Survanta are not "the same drug" is in the section of labeling headed "Infasurf versus Survanta" as set out in the FDA's version of the physician labeling. That section contains a paragraph headed "Acute Clinical Effects" which states:

> Marked improvements in oxygenation and lung compliance may occur shortly after the administration of Infasurf. All controlled clinical trials with Infasurf demonstrated significant improvements in fraction of inspired oxygen ($F_IO_2$) and mean airway pressure (MAP) during the first 24 to 48 hours following initiation of Infasurf therapy.

The quoted sentences were composed by the FDA in substitution of more detailed wording that had been submitted earlier by ONY. While ONY believes its language is preferable to those "minor editorial changes" requested by the FDA, your letter indicates that under both the draft physician labeling presented by ONY and as revised by FDA the drug is safe and effective for use as recommended.

The above-referenced FDA drafted paragraph reveals the occurrence of "marked improvement...during the first 24 to 48 hours following initiation of Infasurf therapy" in all controlled clinical trials. The studies involved comparison of Infasurf with Survanta and with Exosurf. With Infasurf there was "significant improvement... during the first 24 to 48 hours following initiation of Infasurf therapy," when it was compared to either of the other two surfactants. (There was no placebo control in any of the studies). This paragraph reveals that even if Survanta and Infasurf were to be considered the "same drug," compositionally, at the very least the acute clinical effects of Infasurf in the time frames cited justify application of the standards of 21 C.F.R. §316(b)(3)(iii) and constitute a showing that Infasurf provides a significant therapeutic advantage and is clinically superior for purposes of Orphan Drug exclusivity. At a meeting with the Pulmonary Division on February 26, 1997, senior academic clinicians, experienced in neonatal intensive care and clinical trials of lung surfactants, expressed the view that Infasurf was clinically superior to Survanta under 21 C.F.R. §316.31(b)(iii).

Both Survanta and Infasurf are surfactants, each shown to be safe and effective in the prophylaxis and treatment of RDS in premature infants. The drugs share certain qualities but they are not "the same." The fact that FDA review has determined the proteins are active in Infasurf but not shown to be active in Survanta, that different established names have been assigned to each by USAN and accepted by the FDA, and that there are differences in patient responses which make a potentially significant contribution to the welfare of patients in the judgment of qualified experts, necessitate the conclusion that the tentative approval given Infasurf be immediately changed to a final approval. To conclude otherwise would contravene the expressed Agency intent to limit orphan drug exclusivity where there are clinical differences shown between drug products.

In additional to these arguments, we have previously submitted compositional, biophysical, philological, pharmacological and clinical data which also support our contention that Infasurf and Survanta are different drugs under the orphan drug regulations.

We request an appointment with you as soon as possible to bring this matter to an administrative resolution, the optimal solution for both the company and the Agency.

Sincerely,

Edmund A. Egan
President

cc: Drs. Lumpkin and Jenkins and Ombudsman Morrison

NDA 20-521

APR 18 1997

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

Attention: Edmund A. Egan, M.D.
President

Dear Dr. Egan:

Please refer to your July 27, 1995 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Infasurf (calf lung surfactant extract) Intratracheal Suspension.

We also refer to your July 19, 1996 submission, the Agency's September 26, 1996 letter, your November 14 and December 24, 1996 submissions, the Agency's January 13, 1997 letter, your February 12, 1997 submission, and the February 26, 1997 face-to-face meeting between ONY/Forest and this Division.

Further reference is made to your March 14, 1997 submission which contains the amended protocol for an

We also acknowledge your April 4, 1997 telephone facsimile from Dr. Richard Trout. We have reviewed these submissions and have the following general comments and recommendations.

1. With regard to the definitions of equivalence, both to Infasurf and Survanta, such a definition is most reasonably expressed as the percent of drug activity that could be lost (by the modified formulation) and still be considered equivalent to the original drug.

2. All of the statistical testing which you are planning to perform on the results from the studies, as well as the basis for the sample size ("n") that you have

3. The submitted protocol is somewhat ambiguous as to whether activity values for normal lung, depleted lung and original surfactant will be generated in the experiment or based on historical data. All these values should be generated as part of the experiment.

4. We note that the protocol states the specific amount of SP-C and SP-B that will be added to Infasurf and Survanta lipids. Since these modified formulations should have equivalent amounts of proteins to the original surfactant used in the experiment, the amount of proteins to be added to the lipids cannot be pre-specified. Rather, these amounts should be based on your assays of the protein content of the unmodified surfactants actually used in the experiment. The "removed" and "added" proteins should be fully characterized. Please refer to comment #2 from the Agency's September 26, 1996 and January 13, 1997 letters.

5. The protocol states that each preparation will be tested on 8 different lungs; however, there is no indication as to the number of preparations that will be tested. If you are, in fact, planning to test only one preparation 8 times, this raises concerns in that the measures of variability that you will generate relate to variability of the rat lung and procedures for carrying out the experiment and not the variability of the technical preparation of the formulations. It would be preferable to test multiple formulations as well as using multiple lungs to test each formulation. Also, please state clearly how the data will be generated, i.e., assessing "normal", "lavaged" and "treated" state in turn on each lung *versus* assessing 8 "normal", 8 "lavaged" and 8 "treated" lungs.

6. The protocol states that the experiments will be blinded within surfactant but not across surfactant. It is unclear what the logistic reasons are and what delays will be incurred if the study is blinded across surfactants as well. Because it is important to ensure that all aspects of the experiment are carried out in the same manner for both surfactants and without bias, it is preferable to blind the study across surfactants as well.

7. The protocol appears to place the primary weight of evidence of activity on the experiment with minimal discussion of the experiment. If the results of these two methodologies for looking at activity are not consistent in the conclusions that can be drawn, you will need to justify, in your study report, why one methodology rather than the other should be viewed as primary.

8. The definitions of activity provided for the experiment appear to focus on the point estimate rather than provide confidence limits for the various definitions provided. In addition, the protocol appears to pre-specify the definition of fully active. As discussed above, the definition of fully active should be based on the activity of original surfactant actually used in the experiment. The definition of equivalent should then describe the limit of activity that could be lost and still be considered equivalent to the original surfactant.

Should you have any questions, please call Ms. Betty Kuzmik, Project Manager, at (301) 827-1051.

Sincerely,

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA 20-521
HFD-570/Division File
HFD-570/Kuzmik/04-11-97
HFD-570/Schumaker/04-14-97
HFD-570/Himmel/04-16-97
HFD-570/Pina/04-16-97
HFD-570/Nashed/04-11-97
HFD-570/Poochikian/04-14-97
HFD-570/Aras/04-14-97
HFD-570/Wilson/04-16-97
HFD-570/Jenkins/04-16-97
HFD-102/Bilstad/Ripper
HF-53/McCormick (orphan drugs)

/S/
4-17-97

R/D BY: BKuzmik/04-07-97
F/T BY: LSlaybaugh/04-17-97

GENERAL CORRESPONDENCE (GC)

/S/
4/14/97

APPEARS THIS WAY
ON ORIGINAL

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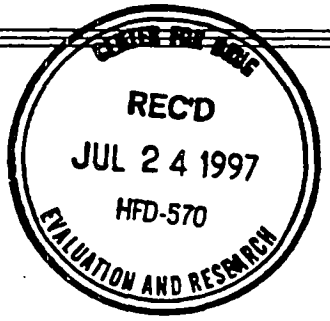
July 21, 1997




Janet Woodcock, MD
Director, Center for Drug Evaluation and Research
HFD - 001
Food & Drug Administration
5600 Fishers Lane
Rockville MD 20857

**RE: Response to Dispute Resolution under 21 CFR §314.103 of July 15, 1997**

**Product: Infasurf (calfactant)**

Dear Doctor Woodcock,

I have carefully read your letter of July 15, 1997 (and the accompanying memoranda by Dr. Jenkins) which declined to adopt ONY's March 14, 1997 request for addressing the scientific/medical dispute of "same drug" status utilizing the mechanism provided by 21 CFR 314.103(b)(3) and instead relied on *ex parte*, in house input. I appreciate your kind words at the end, but must confess that you mistake FDA's total control of the review process for patience on my part.

To be forthright and candid, the reasons in your letter for rejecting our appeal are quite simply wrong. Your letter does not explain why the Agency, despite our repeated importunings, chose not to recruit and utilize outside experts in lung surfactant, which is a highly specialized area, or in neonatology to resolve the scientific dispute. I still do not believe that any knowledgeable, independent experts in lung surfactants and neonatology would endorse the scientific conclusions in your letter. Specifically:

**Composition and Activity Differences Between Infasurf and Survanta:**

(1) There are qualitative and quantitative differences between Infasurf and Survanta and the Agency's refusal to recognize their existence and significance is scientific error. The decision that quantitative differences between Infasurf and Survanta are irrelevant for differentiating the two drugs is not supported by existing scientific knowledge. The amounts, not the "nature" or the "essence", of substances are what produce biological effects - both beneficial and toxic. The presence of inactive, trace amounts of a substance does not mean there are not qualitative differences. To hypothesize biological activity to components with such minuscule, barely detectable, trace amounts flies in the face of scientific common sense these that there exists a threshold below which components are inactive. The differences in 3 of the 6 components referred to in your letter vary by 200% to 4,000% between the products. Further, these differences are directly related to differences in the nature of the production processes for the two surfactants. The Agency's testing proposal, to prove what is already obvious to independent scientific experts, is impossible to perform. The conclusion of the division (that your letter endorsed) is that, despite these qualitative and quantitative differences, the two products have the same "principal molecular structural features," is incompatible with current scientific knowledge of lung surfactants and could not convince independent experts that it is a valid comparison of these two products.

(2) Your use of "clinical activity" as the only functional analysis that is relevant to determining if the compositional differences are meaningful and significant is also inconsistent with the known pharmacology of surfactants. Extensive data have been provided that the compositional differences between Infasurf and Survanta produce significant differences in biophysical activity, physiologic effects and pharmacologic activity. The requirement that only long term outcome differences, proven in clinical trials (a requirement developed by the Agency after Infasurf's NDA submission), are appropriate for determining whether composi-

tional differences are "relevant" stands opposed to the general practice of using extensive preclinical analysis and testing to develop much of what is known about virtually every pharmacologic agent.

(3) The active moiety of a lung surfactant is the dynamic surface film that it creates. That film is an entity, the "active moiety" of the drug. When important components of the film differ substantially in their components, different active moieties are created. ONY has tried to communicate to the Agency that biophysical and biological testing by recognized methods of a lung surfactant can be sensitive enough to detect differences between two lung surfactant preparations that have significantly different active moieties. When two lung surfactants do have consistent and significant differences in these biophysical and biological test systems they cannot have the same "active moiety."

**Clinical Superiority of Infasurf over Survanta**

(1) Your letter and Dr. Jenkin's memoranda are inaccurate in their assertion that the physiologic endpoints of FiO2 and MAP (integrated and averaged for the acute phase of the disease, 0-72 hours) are of unknown clinical significance. These endpoints are the objectives of surfactant therapy and are carefully monitored by physicians using surfactants and are the clinicians way of evaluating the severity of RDS is patients. By logistic regression FiO2 and MAP are each, independently, strongly correlated to the outcome of mortality in infants who have RDS. The correlation is statistically significant, ($P < 0.001$) by logistic regression, controlling for birth weight, the other major determinant of mortality in clinical studies of premature infants. This correlation was replicated in the ONY sponsored Exosurf-Infasurf comparison trial for treatment of RDS. The correlation is equally strong and true whether the patients received Survanta, Exosurf or Infasurf. The clinical significance of FiO2 and MAP in RDS is known, and, therefore, your statement is scientifically wrong. Independent, knowledgeable experts would agree these endpoints are clinically significant.

To no neonatologist's surprise, the more severe the acute respiratory failure during the course of RDS, the more likely a premature infant is to die. These associations have been submitted to the reviewing division, but it appears the relationship between severity of RDS and death were not judged to be important during its internal review. These correlations were submitted to you on June 11, 1997 to support the scientific basis for the validity of the subset evaluation of the treatment group of the infants with persistent and severe RDS presented .

(2) Your letter states the Agency's conclusions that the differences between Infasurf and Survanta in the direct clinical comparison trials do not equal "clinical superiority." I believe that physicians who care for neonatal intensive care patients or parents of premature infants with respiratory failure from RDS would have a different opinion. It was an a priori assertion of the Infasurf-Survanta comparison study that it was not designed or intended to determine differences in efficacy outcomes of death or chronic lung-disease. FiO2 and MAP, as measures of severity of RDS, were prospectively defined endpoints. The division's review focuses only on methodology of analysis, rather than on whether a study, designed for one purpose, allows insight, if not certainty, of other outcomes. No mention is made in Dr. Jenkins memoranda of insights possible by evaluating the Infasurf-Survanta comparison trials in context of what has been learned from Survanta-Exosurf and Infasurf-Exosurf clinical comparison trials.

Because my principal vocational is that of an academic neonatologist, I have a perspective that focuses narrowly on my own patients and their cohorts and I may lack a wide enough vision of FDA's mission to be able to understand how the Agency, whose primary purpose is to improve the public health, can make a "same drug" decision that is so unfriendly to premature infants. There exists a substantial possibility (acknowledged in your letter) and from my vantage point a certainty, that a significant number of premature infants born between June of 1997 and July of 1998 will have suboptimal outcomes as a result of the general unavailability of Infasurf - and given the Agency's recognition of the safety and efficacy of Infasurf, there is

no possibility of any premature infant benefiting from withholding Infasurf until July 1, 1998, but there is a definite possibility of such infants benefiting if it were available today.

**Interpretation of Orphan Drug Regulations**

As we stated at the meeting, the Agency's use of this rule is incompatible with the narrow intent of the macromolecular regulations and with the actual differences between both the large and small molecules in Infasurf and Survanta. The Agency first stated Infasurf was "the same" drug as Survanta using 21 CFR 316.3(b)(13)(ii)(D) in a refusal to file letter of May 7, 1995. At a meeting on July 6, 1995 to discuss this decision, it was obvious that the Agency reviewers were scientifically unsophisticated in lung surfactant chemistry, biophysics, physiology and pharmacology when they made this decision. In all the communications since that time, and again in your letter, the attributes of surfactants that make them "closely related", "complex" and "partly definable" have been used in the mistaken justification of this decision.

This regulation was not intended for this purpose, as is stated in your letter, "We agree that the orphan drug regulations do not identify a specific regulatory mechanism for determining the sameness in the case of Infasurf and Survanta." Therefore, I believe the Agency is required to follow the "usual" or small drug methodology because the prologue to the regulations "...regards two drugs as different if they differ with respect to the chemical structure of their active moieties. First, such differences are highly likely to lead to pharmacologic differences. Second, the development of an agent with a novel active moiety is not a financially or intellectually trivial matter; it represents a considerable effort and a substantial risk..."[1]

While I greatly appreciate your professional atmosphere and personal cordiality, as well as that of the Agency's staff at the meeting of June 11, 1997, the failure of the Agency to obtain input and advice from scientists knowledgeable about lung surfactants and neonatology, since the submission of the NDA, has resulted in many FDA decisions during the review being arbitrary and capricious. This has been a systematic problem. For example, Dr. Jenkin's memorandum of April 22, 1997 describes the evolution of the "same" drug issue at a series of meetings attended only by division personnel and supervisory Agency staff, none of whom were experts in lung surfactants. My professional academic career has always involved peer review (as a reviewer and as one being reviewed) of scientific proposals and completed projects. Essential to fairness are reviewers who are unbiased and work within the limits of their expertise. I cannot understand why the Agency has been unwilling to utilize outside consultants to advise it on the "same drug" issue from a scientific and clinical perspective.

The Agency frequently seeks the advice of outside experts, even in areas where it has more staff expertise that it has in lung surfactants and neonatology. It is, indeed, difficult to avoid the conclusion that the Agency, for whatever internal reasons, did not want the enlightenment that independent experts could provide. I again urge the Agency to consult with impartial experts or convene an advisory committee to review this ill informed decision. To fail to do so is to fail in the Agency's essential mission to protect the health of the American people.

Sincerely,

Edmund A. Egan, MD
President

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1. 56 FR 3341, January 29, 1991.