DEC 19 1997

NDA 20-521

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 (calfactant) Intratracheal Suspension.

Reference is also made to the Agency's letter dated September 26, 1996, the Division's memorandums to Dr. Janet Woodcock dated April 22 and July 2, 1997, and the Agency's letter dated July 15, 1997.

Further reference is made to your submission dated September 24, 1997, in which you submitted a copy of a recent publication which reports the results of a study conducted by et al. The study by et al. evaluated the

You state in your submission that this study provides further support for your claim that Infasurf and Survanta are "different" drugs with regard to orphan drug exclusivity. You further state that you "believe that the publication of this new study makes the Agency's assumption that SP-B is at active levels in Survanta inconsistent with all the scientific data available."

We have carefully reviewed your September 24, 1997, submission, including the publication by et al., and we do not agree with your position that these new data are adequate to support a change in the Agency's position that Infasurf should be considered to be the "same" drug as Survanta for purposes of orphan drug exclusivity. As stated in the Agency's letter dated September 26, 1996, if it can be demonstrated that a specific 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, Infasurf and Survanta may be deemed to be "different." The

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

Sincerely,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 20-521
HFD-570/Division File
HFD-570/Kuzmik
HFD-570/Schumaker 12/19/97
HFD-570/Pina
HFD-570/Himmel
HFD-570/Nashed
HFD-570/Poochikian

Drafted by: BKuzmik/12-02-97
Reviewed by: MPina/12/2-97; MHimmel/12-2-97; JJenkins/12-3/97;
JBilstad/12-12-97; LDickinson/12-17-97;
CSchumaker/12-18-97
FT: PWilson/12-18-97
WORD

GENERAL CORRESPONDENCE (GC)

/S/
12/19/97

/S/
12/5/97

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 18, 1995

Charles P. Hoiberg, PhD
Acting Director
Division of Oncology and Pulmonary Drug Products
Office of Drug Evaluation I
Food and Drug Administration
HFD - 150
5600 Fishers Lane
Rockville, MD 20857

RE: INFASURF, NDA 20-521

Dear Dr. Hoiberg:

We are in receipt of your letter of May 10 advising us that under 21 CFR §316.3(b)(13)(ii)(D) you are refusing to file the above referenced NDA.

The reason given in your letter for such an action is that "the Agency has determined that Infasurf and Survanta are the "same drug" as defined by 21 CFR §316.3(b)(13)(ii)(D)."

It is our position that Infasurf and Survanta are not the "same drug." There exists extensive information, including that available in the public domain, that the totally natural surfactant Infasurf (calf lung surfactant extract) is not the same drug as the semi-synthetic surfactant Survanta (beractant). In fact, Infasurf is different from Survanta, just as Survanta is different from Exosurf Neonatal (colfosceril palmitate, cetyl alcohol, tyloxapol), both of which presently have separate Orphan Drug approvals.

In addition we believe that there is no justification for the FDA to refuse to file the Infasurf NDA. The existence of an Orphan Drug approval for a drug does not constitute grounds under §314.101(d) or (e) for refusing to file another NDA during the period of the Orphan Drug's exclusivity. The law provides only that the Agency "may not approve another application *** for such a drug for such disease or condition *** until the expiration of seven years from the date of the approved application***" (emphasis added). Thus, the Infasurf NDA is entitled to be filed and should be reviewed while the "same drug" issue is being considered.

We respectfully request at this time that the Agency proceed with the review of Infasurf. Independently of the NDA review, we request that the Agency schedule a meeting which will provide us the opportunity to discuss the "same drug" issue with the appropriate FDA personnel, including Dr. Robert Temple, Director of the Office of Drug Evaluation I and Dr. Martin Himmel, Supervisory Medical Reviewer, both of whom participated in earlier discussion regarding this product.

Please provide us as soon as possible with available date for a meeting to be held between mid-June and June 30, 1995. We will call you before the end of May to set a definite date and to provide you with the identity of the person who will attend on behalf of ONY and Forest.

Sincerely,

ONY, INC.

for Edmund A. Egan, MD

Edmund A. Egan, MD
President

FOREST LABORATORIES, INC.

for Michael M. Rosen, PhD
Director of Regulatory Affairs

MAY 10 1995

C. KUZMA K

NDA 20-521

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

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

Dear Dr. Egan:

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

We have given your NDA a preliminary review, and we find it is not sufficiently complete to merit a complete critical medical and technical review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this NDA under 21 CFR 314.101(d) for the following reasons:

> Survanta (a bovine lung surfactant manufactured by Ross Labs) was approved under the Orphan Drug Regulations on July 1, 1991. The Orphan Drug Regulations provide at 21 CFR 316.31 that "After approval of a sponsor's marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which orphan drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug before the expiration of 7 years from the date of such approval..." Based upon information submitted in the NDA for Infasurf, the Agency has determined that Infasurf and Survanta are the "same drug", as defined by 21 CFR 316.3(b)(13)(ii)(D). This provision establishes 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." In order for FDA to approve the NDA for Infasurf before Survanta's exclusivity expires, you must submit data demonstrating that Infasurf is clinically superior to Survanta, as defined by 21 CFR 316.3(b)(3)(i) and (ii).

While not reasons for refusing to file the application, we have the following comments.

2. We note that a full Environment Assessment (EA) was submitted. As an extract of natural calf lung surfactant, this EA could fall under 21 CFR 25.31a(b)(5) which allows for an abbreviated EA for a substance occurring naturally in the environment. Furthermore, an abbreviated EA would be acceptable under 21 CFR 25.31a(b)(3) since this product has been designated as an orphan drug.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file this application. To file this application over FDA's protest, you must avail yourself of this informal conference. If you have any questions please call:

Betty Kuzmik
Consumer Safety Officer
(301) 594-5720

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file this application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, this application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

Under the Prescription Drug User Fee Act of 1992, FDA would normally refund one-half of the fee submitted with an application (25% of the total fee due). Under the provision for Small Business Exception, your fee will be determined one year from the date that this application was submitted. If you decide to file this application over protest, the filing of this application over protest will be regarded by the Agency as a new original application for user fee purposes, and will be assessed a user fee applicable to a new submission.

Sincerely yours,

/S/

Charles P. Hoiberg, Ph.D.
Acting Director
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-521
HFD-150/Div. files
HFD-150/Himmel
HFD-150/Pina
HFD-150/Poochikian/5-10-95
HFD-150/Ng
HFD-150/DeGeorge
HFD-150/Choi
HFD-150/Wilson
HFD-150/Koutsoukos
HFD-150/Mehta
HFD-150/Gillespie
HFD-150/Schumaker
HFD-150/Betty Kuzmik
HF-35/Vaccari
GCF-1/Dickinson
HFD-80
DISTRICT OFFICE

drafted: BKuzmik/5-4-95
revised by: CSchumaker/5-4-95 and 5-10; MHimmel/5-5-95; PVaccari/5-8-95; LDickinson/5-8-95
final

REFUSAL TO FILE (RF)

APPEARS THIS WAY
ON ORIGINAL

KUZMICK

NDA 20-521

APR 10 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 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Infasurf Intratracheal Suspension

Therapeutic Classification: Standard

Date of Application: March 13, 1995

Date of Receipt: March 13, 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 May 11, 1995 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Betty Kuzmik
Consumer Safety Officer
Telephone: (301) 594-5720

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,

/ST 4/10/95

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

APPEARS THIS WAY
ON ORIGINAL

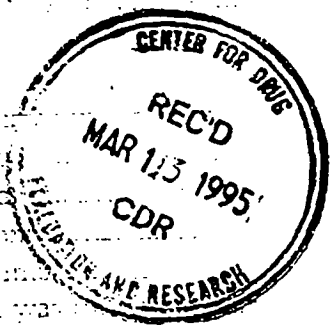
cc:
Original NDA 20-521
HFD-150/Div. Files
HFD-80
HFD-150/Schumaker/4-3-95
HFD-150/CSO/Betty Kuzmik 4/7/95

drafted: kuzmikb/3/28/95
Final typing by:

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

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



March 13 , 1995

Charles P. Hoiberg, Ph.D., Acting Director
Division of Oncology and Pulmonary Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-150
5600 Fishers Place
Rockville, MD 20857

Re: **NDA 20-521/Original New Drug Application**

Product: **Infasurf® (Calf Lung Surfactant Extract) Intratracheal Suspension**

Dear Dr. Hoiberg:

We are submitting an original New Drug Application for Infasurf® (Calf Lung Surfactant Extract) Intratracheal Suspension pursuant to the requirements of section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, 21CFR 314, and supporting Food and Drug Administration guidelines. This submission includes both archival and review copies.

Infasurf® is intended for the prevention and treatment of Respiratory Distress Syndrome (RDS) in neonates. Clinical data is presented for two, randomized, masked, parallel active controlled trials comparing Infasurf® with Exosurf Neonatal®. These studies referred to as the Surfactant Comparison Trial - Prophylaxis (SCT-P) and Surfactant Comparison Trial - Treatment (SCT-T) demonstrate the efficacy and safety of Infasurf® in the prevention and treatment of RDS. The safety has been further demonstrated in open label trials involving over 14,000 infants.

In accordance with our agreement with FDA at the meeting of August 16, 1993 this submission does not contain any case report forms. Hard copies of case report forms and SAS data sets on disks will be provided upon your request. However, this submission does contain death listings from all the clinical trials which can be found in Section 12.

The scope of Section 5: Nonclinical Pharmacology and Toxicology reflects discussions held between Forest-ONY and FDA on February 12, 1992 and March 4, 1992. The decision to limit the kinds of toxicology studies was substantially influenced by the large clinical experience already accumulated. Regarding additional preclinical pharmacology and toxicology requirements, Dr. A. Taylor noted that FDA would be ". . . . flexible on this issue if the benefit of the drug is considered" (FDA meeting minutes of February 12, 1992).

A March 11, 1992 letter to Dr. A. Taylor confirmed a March 4, 1992 telephone conversation between himself and K. Albert, Ph.D. (Forest) in which it was agreed teratology studies would not be required for this NDA. A copy of this letter is included in Section 5.7.

Traditional *in vivo* bioavailability studies of Infasurf® in humans were not done due to the medical fragility of the neonatal population. A request for a waiver of those requirements under 21CFR 320.22(e) is presented in Section 6 and in the clinical pharmacology portion of Section 8.

The information contained in this submission is organized in accord with the Food and Drug Administration Guideline on "Formatting, Assembling and Submitting New Drug and Antibiotic Applications" dated February, 1987. The section numbers are assigned as per Appendix A of that guideline, and the submission is paginated by section. For example, page 08-00123 is page 123 of Section 8: Clinical Data. Once the section is paginated it does not change throughout the submission. Therefore, the Index (Section 1) and Summary (Section 2) maintain the page designation of first use though they appear in each technical section.

The documentation on Sterilization Process Validation is presented per the December 3, 1993 Federal Register. This information has been duplicated from Section 3: Chemistry, Manufacturing and Controls and is formatted as Section 7 per discussion with Dr. Cuny at the Forest/ONY meeting with FDA on November 10, 1993. Section 7 is double paginated in the bottom center of the page and retains the pagination of Section 3 in the lower right corner.

Section 4: Samples, Method Validation and Labeling is extracted from the CMC section. Most of the Section 10: Statistical Data is duplicated from the Clinical section. Four(4) volumes (Vol. 48 through Vol. 51 containing supporting tables from the studies) were added to the statistical section. Therefore, all of Section 4 and most of Section 10 are double paginated and retain their original pagination in the lower right corner of the page.

As required, a field copy of the Chemistry, Manufacturing and Controls (Section 3), Application Summary (Section 2), application form and certification statement is being submitted to the Buffalo, N.Y. district office.

The applicant received orphan drug designation on June 7, 1985 as shown on page 3-454 of the Orange Book for 1994. (see FDA letter attached).

Additionally this product is a new chemical entity which was not previously been subjected for approval by FDA.

This application is submitted by ONY, Inc. Amherst, N.Y., the sponsor and owner of Infasurf®. Pursuant to the small business administration exception to the Prescription Drug User Fee Act of 1992 (21 U.S.C§ 379h(b)(2)), FDA granted ONY, Inc. a deferral of payment of the application fee for NDA #20-521 in a letter of December 14, 1994. Attached is a copy of that letter.

Samples of this product will be provided upon request.

This application was prepared in cooperation with Forest Laboratories, Inc., NY, N.Y. who has marketing rights to the product as ONY's agent. If you have any questions at any time in your review concerning the material submitted, we would be pleased to discuss them with you by telephone or in person. Please contact Dr. Michael M. Rosen at (212) 421-7850. Correspondence regarding this application should be addressed to:

Michael M. Rosen, Ph.D.
Director of Regulatory Affairs
Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022-4731

Sincerely,
ONY, Inc.

Edmund A. Egan, MD
President

MEMORANDUM

DATE: April 22, 1997

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

THROUGH: James Bilstad, M.D.
Director, Office of Drug Evaluation II, HFD-102

TO: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research, HFD-1

Murray Lumpkin, M.D.
Deputy Director (Review Management), Center for Drug Evaluation and Research, HFD-2

SUBJECT: NDA 20-521 Request for Dispute Resolution under 21 CFR 314.103

On March 14, 1997 ONY Inc., the sponsor of NDA 20-521 for Infasurf (calf lung surfactant extract), submitted a request for dispute resolution to the Office of the Center Director. The issues in question are whether Infasurf is the "same drug" as Survanta (beractant) and whether Infasurf is clinically superior to Survanta. The purpose of this memorandum is to provide the Division of Pulmonary Drug Products' perspective on the complex scientific and regulatory issues related to the Center's determination that Infasurf and Survanta are the "same drug" under the orphan drug regulations and that clinical superiority has not been adequately demonstrated.

BACKGROUND

Survanta Approval and Orphan Drug Exclusivity

NDA 20-032 for Survanta[1] was approved in 1991 for the "prevention and treatment ("rescue") of

[1] The DESCRIPTION section of the Survanta package insert states: SURVANTA® (beractant) Intratracheal Suspension is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitolyphosphatidylcholine), are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant. The resulting composition provides 25 mg/mL phospholipids (including 11.0-15.5 mg/mL disaturated phosphatidylcholine), 0.5-1.75 mg/mL triglycerides, 1.4-3.5 mg/mL free fatty acids, and less than 1.0 mg/mL protein. Its protein content consists of two hydrophobic, low molecular weight, surfactant associated proteins commonly known as SP-B and SP-C. It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A. Each mL of SURVANTA contains 25 mg/mL of phospholipids. It is an off-white to light brown liquid supplied in single-use glass vials containing 8 mL (200 mg phospholipids).

Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants." Survanta was granted 7 years of marketing exclusivity under the orphan drug regulations; the period of exclusivity expires on July 1, 1998.

Regulatory History of NDA 20-521 (see the attached Administrative Review of and NDA 20-521)

ONY Inc. originally submitted NDA 20-521 for Infasurf on May 13, 1995. During the initial filing review, the issue of Survanta's orphan drug exclusivity was raised and a review was conducted to determine if Infasurf was the "same" or "different" from Survanta based on the orphan drug regulations. The Division and Office concluded that the two surfactants were the "same drug" under the orphan drug regulations (see below for the scientific and regulatory rationale for this decision). An overview of the clinical trials submitted in the original application revealed no studies that could support an evaluation of possible clinical superiority of Infasurf over Survanta. Following further consultations with Dr. Bilstad, Ms. Dickinson from the Office of General Counsel, and Dr. McCormick from the Office of Orphan Drug Products, the Division issued a Refuse to File (RTF) letter for this application on May 10, 1995[2].

ONY expressed their disagreement with the Division's decision and immediately requested a meeting to discuss this issue. At the July 6, 1995, meeting, ONY's legal counsel, Mr. Kaplan, argued that the RTF action was inappropriate and that the application should be filed and reviewed based on the original submission date. Dr. Egan, President of ONY, along with several consultants, argued that Infasurf and Survanta were not the same drug for several reasons, including: 1) Infasurf is prepared as an extract of calf whole lung while Survanta is prepared as an extract of bovine lung; 2) Ross, the manufacturer of Survanta

while ONY does not add any substances to Infasurf; and 3) the levels of SP-B in Survanta are very low and sub-threshold for activity while the levels of SP-B in Infasurf are 20-40 times higher and necessary for Infasurf activity. ONY presented data from the published literature and from their own work, including new preliminary data on comparative SP-B levels in the two products generated after the RTF letter was issued, in support of their

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[2] The stated reason for the RTF action was: "We are refusing to file this NDA under 21 CFR 314.10(d) for the following reasons: Survanta (a bovine lung surfactant manufactured by Ross Labs) was approved under the Orphan Drug Regulations on July 1, 1991. The Orphan Drug Regulations provide at 21 CFR 316.31 that "After approval of a sponsor's marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which the orphan drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug before expiration of seven years from the date of such approval..." Based upon information submitted in the NDA for Infasurf, the Agency has determined that Infasurf and Survanta are the "same drug", as defined by 21 CFR 316.3(b)(13)(ii)(D). This provision established 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." In order for FDA to approve the NDA for Infasurf before Survanta's exclusivity expires, you must submit data demonstrating that Infasurf is clinically superior to Survanta, as defined by 21 CFR 3.16.3(b)(3)(I) and (ii)."

claim of the pivotal role of SP-B in normal surfactant function. Dr. Egan and the ONY consultants expressed their strong personal belief that Infasurf was clinically superior to Survanta and stated that they had completed a clinical trial comparing the two. The data from the trial were not included in the original NDA; however, ONY promised that the final study report would be submitted to the Division for review by mid-July 1995.

The Division, in consultation with Drs. Bilstad and Temple, Ms. Dickinson, and Dr. McCormick, agreed that ONY had presented a credible scientific argument for why Infasurf and Survanta should be considered "different drugs" and that the NDA would be filed for review if ONY submitted the data supporting the pivotal role of SP-B along with data demonstrating the marked differences in SP-B levels between the two surfactants. The "same" versus "different" issue would then become a review issue and would be based on the SP-B argument or the Infasurf versus Survanta comparison trial which the sponsor claimed would demonstrate that Infasurf was clinically superior to Survanta. It was agreed, however, that the RTF action for the original application was correct since the data addressing the "same" versus "different" drug issue (i.e., the SP-B data presented at the July 6, 1995, meeting and the Infasurf versus Survanta trial) were not contained in the original application and were necessary for review.[3]

On July 13, 1995, the Division issued a letter to ONY stating its willingness to file a resubmitted application[4]. ONY resubmitted the application on July 27, 1995, and in the cover letter stated

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[3] At a subsequent meeting of the Center's Refuse to File Review Committee, the Committee concluded that an RTF action is not appropriate in situations where the product that is the subject of the NDA is blocked from marketing due to exclusivity granted to another product. The rationale was that the Center could complete the review of the application and if all other regulatory requirements for approval were met, could issue an action letter with final approval delayed pending expiration of the exclusivity.

[4] The conditions listed in the letter were: "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 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."

their commitment to provide validated comparative data for SP-B for the two surfactants by December 1, 1995. The application was filed by the Division with the resubmission date as the date for calculation of the User Fee Goal Date.

Further internal discussions of the "same" versus "different" drug issue occurred in a meeting on March 4, 1996, which included Drs. Temple, Botstein, Bilstad, and McCormick in addition to representatives from the Division. The participants at the meeting agreed that the available data on Infasurf and Survanta did not support a conclusion that they were "different" drugs under the orphan drug regulations. It was agreed that the SP-B data that ONY had promised to generate (and which had not yet been submitted) were critical to ONY's argument. It was further agreed that if both surfactants were shown to contain SP-B, albeit at different levels, it might be necessary for ONY to provide data demonstrating the significance of the differences in SP-B levels with regard to activity of the surfactants. At a subsequent meeting, similar conclusions were reached with regard to Curosurf, a porcine derived surfactant under development by Dey Laboratories. ONY was informed of these conclusions at a meeting held on March 20, 1996, to discuss orphan drug and CMC issues related to NDA 20-521. In that meeting, ONY and its consultants expressed surprise that this "new" requirement was being requested since they had felt that the orphan drug issue was resolved with their agreement at the July 6, 1995, meeting to provide a validated comparative assay of SP-B levels in the two surfactants. The Division made clear to ONY at the March 20, 1996, meeting that the "same" versus "different" drug issue was a review issue and that a final decision had not yet been made (again the comparative data for SP-B levels in the two surfactants had not yet been submitted by ONY). ONY was also informed that the issue was scheduled to be discussed at a Center level meeting in the near future and that they would be informed promptly of the results of that meeting.

Center level discussions of the orphan drug issues related to NDA 20-521 occurred at an April 24, 1996, meeting attended by Drs. Woodcock, Lumpkin, Temple, Bilstad, McCormick, Ms. Dickinson, Ms. Axelrad, Mr. Hare, and Division representatives. The participants concurred with the Division/Office assessment that Infasurf and Survanta were the "same" drugs under the orphan drug regulations.[5]

Dr. Egan was informed of these Center level decisions in a telephone conversation held on April

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[5] The conclusions from the meeting minutes were: "1.Survanta, Infasurf and Curosurf are the "same" drug under the Orphan Drug Regulations. To prove that Infasurf is different from Survanta the sponsor must provide quantification of SPB and proof that the level of SPB in Survanta is inactive. The same approach would apply to Curosurf; 2) Dr. Jenkins will notify ONY and Dey Labs of these Center level determinations. The Commissioner's Office will be notified by Dr. Lumpkin of this issue; 3) The Division will not refuse to file the Curosurf NDA.

5) The therapeutic equivalence code for Survanta, Infasurf and Curosurf will be the same once approved, however, they will be listed as not interchangeable."

26, 1996, and in a letter issued by the Division on May 24, 1996.[6]

On July 25, 1996, the Division issued an approvable letter to NDA 20-521, which listed one clinical and 20 CMC deficiencies. In the letter, the sponsor was reminded of the orphan drug exclusivity of Survanta and the fact that the NDA could not be approved prior to July 1, 1998, unless the sponsor demonstrated that the two drugs were not the "same" with reference to the May 24, 1996, letter.

On July 19, 1996, ONY submitted a draft in-vitro protocol to demonstrate that Infasurf and Survanta were not the "same drug" based on the "active moiety" approach outlined in the May 24, 1996, letter. On September 26, 1996, the Division sent a letter to ONY that provided Division comments on the draft in-vitro protocol submitted on July 19, 1996. The Division agreed with the overall approach of demonstrating that a 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.[7] On November 14, 1996, ONY submitted a revised in-vitro protocol that contained their responses to the Division's September 26, 1996, comments. On January 13, 1996, the

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[6] The body of the letter stated: "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 micro-molecular 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."

[7] Comments provided included; 1) all procedures and tests should be in replicate on both drug products under the same experimental conditions; 2) all methods should be properly described and validated, the modified surfactants should be adequately characterized and quantitated; 3) the biologic testing should include both the and the 4) all tests and measurements should be conducted in a randomized and fully blinded fashion; and 5) a detailed protocol of the experimental plan and plan for analysis of the data should be submitted for review prior to initiation of the studies. The protocol should include a pre-specified definition, rationale and in-vivo data-based justification of what will be considered a meaningful difference, or lack thereof, between formulations.

Division sent a letter to ONY that provided Division comments on the revised in-vitro protocol[8]. ONY submitted a response to the comments on February 12, 1997.

In its November 14, 1996, submission, ONY also submitted the results of a reanalysis of the Infasurf versus Survanta trial, which the sponsor contended support a conclusion that Infasurf is clinically superior in terms of safety and effectiveness to Survanta[9]. (Note: If a subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.) The sponsor also requested a meeting with the Division to discuss this issue and suggested that "ad hoc specialists in neonatology" be included. In further support of their argument that the clinical differences observed between Infasurf and Survanta in this trial were adequate to meet the standard of the orphan drug regulations, the sponsor referenced a decision by the U.S. District Court in the case of Berlex vs FDA et al.[10]

The Division conducted a review of the reanalysis of the Infasurf versus Survanta trial and the facts regarding the Berlex vs FDA case with input from Dr. Bilstad, OGC, and Orphan Drugs and concluded that the data did not support a conclusion that Infasurf was clinically superior to Survanta (see below for a detailed analysis of the data). It was also agreed that a meeting was not necessary on this issue. Dr. Egan was informed of the Division's decisions by telephone on

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[8] The comments provided on the in-vitro protocol were: 1) Same testing methods, procedures and conditions should be applied to all Infasurf and Survanta preparations; 2) A detailed analysis of the components of the modified surfactants would be provided; 3) The level of each "depleted" component should be lowered significantly, at least 10 fold and reconstitution with the "depleted" component should be based on the baseline levels; 4) All preparations should be tested a clear and comprehensive plan for data analysis, including assessment of "activity" of each preparation would be provided; 5) The assessment of "active" and "inactive" should be based on an in-vivo data-based justification for meaningful differences; 6) Protocol should specify the number of lots and number of preparations to be tested, number of replicates, etc.; 7) Sample sizes should be clearly stated and should be based on a two-sided alpha level of 0.05 and 80% power; 8) A definition of equivalence should be developed and hypothesis tested appropriately; 9) Prospectively state how the p values for the and will be combined

[9] The clinical/statistical review of the Infasurf versus Survanta trials as originally submitted to NDA 20-521 concluded that: 1) for the prophylaxis trial; Infasurf was significantly worse than Survanta on the endpoints of all cause mortality and mortality due to respiratory causes and comparable to Survanta for prevention of RDS, 2) for the treatment trial; Infasurf was comparable to Survanta on all clinically relevant efficacy endpoints. For safety, Infasurf patients had a significant increase in adverse events during surfactant administration (airway obstruction/suctioning) over Survanta patients. The overall conclusions of the review were that Infasurf was not superior to Survanta for any clinically relevant outcome measure, for most outcome measures the two products were comparable, and for a few outcome measures (i.e., all cause and respiratory mortality in the prophylaxis trial and adverse events during drug administration) Infasurf was inferior to Survanta.

[10] In that case, the court upheld an FDA determination that a beta-interferon preparation for treatment of mutliple sclerosis was clinically superior to an existing product covered by orphan drug exclusivity based on a reduced rate of injection site adverse reactions, including a lower incidence of local skin necrosis and limb amputations.

December 9, 1996. Dr. Egan expressed his disagreement with the Division's conclusions.

On December 24, 1996, Dr. Egan submitted a letter to the Division in which he expressed concerns about the timeline for completion of the review of the Infasurf NDA. Dr. Egan again expressed his belief that ONY had sufficiently demonstrated that Infasurf was a "different" drug from Survanta and that they had also demonstrated that Infasurf was clinically superior to Survanta. Dr. Egan stated that "we have been continually frustrated by the changes in requirements put forth by the Agency with regard to chemistry and product differentiation issues" and also expressed his frustration that their "repeated" requests for a face-to-face meeting on these issues with participation by expert neonatologists had not been granted. Attached to the letter was a timeline of NDA 20-521, which described the sponsor's views of the events that had occurred since the NDA was first submitted (Note: an updated version of this timeline was included as an attachment to the March 14, 1997, letter to Dr. Woodcock). Dr. Egan requested rapid feedback on the in-vitro protocol from the Division and requested a meeting with the Agency.[11]

The December 24, 1996, letter was discussed with Dr. Bilstad who expressed his continued support for the Division's conclusion that the available data do not support a conclusion that Infasurf is clinically superior to Survanta. Dr. Bilstad further agreed with the Division's plan to offer the sponsor a meeting to discuss the in-vitro product differentiation and clinical superiority issues. The meeting offer was included in the Janaury 13, 1997, letter to ONY (see above) and the meeting was scheduled for February 26, 1997. (Note: The Division was available to meet at an earlier date; however, Dr. Egan requested a later date to allow him more time to present his clinical argument.)

At the February 26, 1997, meeting, ONY was told that the Division was in general agreement with ONY on the proposed in-vitro product differentiation protocol; however, the Division expressed its continuing concern with the limited documentation/validation of the methods to be utilized and the defintions and analysis procedures proposed by ONY for how the in-vitro excised data would be interpreted with reference to "active", "inactive", "equivalent", etc. The Division advised ONY to insure that their methodology were as scientifically rigorous as possible to faciliate regulatory decisions based on the data obtained. The Division expressed its inability to agree a priori to the sponsor's proposed analysis plan given the unprecedented nature of the studies to be performed, the limited information available in support of the methodology and sensitivity of the assays to be used, and the rather wide definitions of "equivalence" proposed by the sponsor. ONY expressed frustration that they could not get

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[11] The text of the letter included the following statement: "if necessary, we request an urgent meeting to address all outstanding chemistry and product differentiation issues so that ONY can provide the Agency with the information needed to grant marketing approval for Infasurf. In the meantime, we are convinced that a substantial cohort of infants with RDS, who progress to persistent, servere respiratory failure even when treated with the currently approved surfactants, would uniquely benefit from the availability of Infasurf. These infants are thus adversely affected by continuing delays of its approval."

agreement on these issues and their concern that the studies may not support an Agency decision. Dr. Bilstad acknowledged the sponsor's concerns; however, he reiterated the numerous issues that preclude a priori agreement on how the data from the proposed studies will be interpreted.

ONY also presented their case in support of the clinical superiority (safety and effectiveness) of Infasurf over Survanta. This conclusion was based on a combined analysis of several large Phase 3 trials as well as their reanalysis of the Infasurf versus Survanta trial. Three neonatology consultants to ONY expressed their individual opinions that Infasurf was clinically superior to Survanta and their frustration that this better drug was being blocked from approval. One of the neonatologists acknowledged, however, that there were not adequate data to support a conclusion by the Agency that Infasurf was clinically superior to Survanta. The Division stated the basis for its conclusion that the data presented by ONY were inadequate to support a conclusion that Infasurf was clinically superior to Survanta (see below). Dr. Bilstad expressed his agreement with the Division's conclusion and stated that the final orphan drug regulations state that generally the level of support necessary to demonstrate clinical superiority for orphan drugs is the same as that required by the Agency to support a comparative labeling claim for a drug. He pointed out that this is a fairly high standard. Dr. Bilstad also informed the sponsor that these Division/Office level conclusions could be appealed by ONY to higher levels within the Center and that he planned to raise these issues to higher levels within the Center himself.

Division Position on Orphan Drug Issues

"Same" versus "different" drug

Infasurf and Survanta, like natural mammalian surfactant, are complex mixtures of lipids and proteins and it appears that it is the interaction between the various components that is responsible for their physiologic activity and clinical effects. The very nature of these complex mixtures and the complex interactions that occur between the components make it very difficult to ascertain and identify each of the specific "active" components of the mixture; rather the mixture as a whole is active. When analyzed by specific components; e.g.,. phospholipids, neutral lipids and proteins, Infasurf and Survanta generally contain the same components, albeit in differing amounts or concentrations for some of the components. It is very difficult to determine the relevance of these differences in concentrations of individual components given that the two products are both active in-vitro and in-vivo and since the specific threshold level for activity of individual components is not well described. In addition, many of the individual components appear to play complimentary roles with regard to surfactant activity such that decreases in one component in a given surfactant, or a given batch of a surfactant, may be offset by increases in another component with maintanence of overall surfactant activity.

For purposes of determination of "same" versus "different" drug as defined under the orphan drug regulations, it is clear that Infasurf is intended for the same use as the previously approved drug, Survanta; i.e.,. the prophylaxis and treatment (rescue) of neonates with RDS. The final orphan drug regulations do not specifically address a regulatory mechanism for determining that a drug is the "same" as a previously approved drug for drugs like Infasurf and Survanta, which

are comprised of complex mixtures of both large and small molecules. The orphan drug regulations do describe definitions and examples for making such determinations for small molecules and for large molecules (macromolecules). It is the Division's position that the most appropriate analysis of surfactants is analagous to the analysis applied to macromolecules and specifically the example given in 21 CFR 316.3(b)(13)(ii)(D) since Infasurf and Survanta are complex, partly definable mixtures of small (lipids) and large molecules (proteins)[12]. Such an analysis, in the Division's opinion, makes naturally derived surfactants the "same" and places the burden of proof on the sponsor of the second product to justify why the two products should be considered different or to demonstrate clinical superiority of the second product.

ONY has argued that Infasurf and Survanta are manufactured differently (i.e., Infasurf is an extract from whole lung of calf lungs while Survanta is an extract from a bovine lung and that the levels of certain components (i.e., disaturated phosphatidycholine , are adjusted during the manufacturing of Survanta to compensate for lipids and surfactant-associated proteins lost during the manufacturing process. ONY argues that these differences in manufacturing result in products that are not the "same". The Division disagrees with this position since, in the end, the two products remain complex mixtures of lipids and surfactant-associated proteins, albeit with differing concentrations of individual components, that exhibit surfactant activity in-vitro and in-vivo and are intended for the same clinical use. It does not seem particularly relevant to the determination of "sameness" that some of the lipids in Survanta are not naturally derived. Reliance on an interpretation of "different" drug based simply on differences in the manufacturing process or the source of the components in the final product would make it very easy for a second sponsor to develop a "different" drug in the case of surfactants and would undermine the intent of orphan drug exclusivity. The Division recognizes it is possible that such modifications could result in a better product (i.e., safer or more effective); however, the Division believes that the burden of proof should be on the sponsor to support such claims with valid scientific data and that in most situations this would require clinical data.

ONY has also argued that Infasurf should be considered "different" from Survanta based on the reported 20-40 fold difference in SP-B levels between the two surfactants. This argument presumes that the amount of SP-B in Survanta is sub-threshold and not necessary for Survanta's activity while the much higher amount of SP-B in Infasurf is active and necessary for Infasurf's activity. The Division has agreed to the application of such an "active moiety" concept to a particular component of surfactants and has advised ONY that in support of such a claim it would be necessary to demonstrate 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. In support of their argument that the level of SP-B in Survanta is sub-threshold, the

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[12] 21 CFR 316(b)(13)(ii)(D) states: Closely related, complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, would be considered the same unless the subsequent drug was shown to be clinically superior.

sponsor has referred to a published study by Mizuno et al.[13] In that study the investigators compared the pressure-volume curves in premature lambs following treatment with Survanta, Survanta + 0.5% SP-B, Survanta + 2.0% SP-B, natural sheep surfactant, and no treatment. The authors report that the mean pressure-volume curves of Survanta and Survanta + 0.5% SP-B treated animals were significantly improved versus control; however, they were significantly less than the mean pressure-volume curves for natural sheep surfactant and Survanta + 2.0% SP-B treated animals. The sponsors also reported parenthetically that "in-vivo function of lipid-extracted Survanta was not different from that of Survanta (data not shown)." The authors of the study concluded that "These results demonstrate that there is insufficient SP-B in Survanta for optimal function immediately after treatment" and that "These results are consistent with the critical role of SP-B in surfactant function."

While on the surface the results of this published study appear to provide support for ONY's assertion that the levels of SP-B in Survanta are sub-threshold, there are several factors that must be considered in interpreting the results with regard to a regulatory decision to find that Infasurf and Survanta are not the "same" drug. Some of the factors include: 1) the published article only briefly describes the methods that were used to prepare the SP-B extracts that were added to Survanta and provides little information regarding the methods used to analyze the resulting extracts for purity and SP-B content prior to addition to Survanta for in-vivo testing; 2) the article provides no information on how the "lipid-extracted" Survanta (presumably intended to be protein free), which the authors report was "not different from Survanta", was prepared or analyzed, nor any data for the in-vivo testing of this preparation; 3) the article makes no reference to the data analysis plan, sample size calculations, methods to correct p values for multiple endpoints, etc. used in the study; and 4) the study did not address the role of SP-B in Infasurf in the same in-vivo model; i.e., there were no tests performed of "lipid-extracted" Infasurf. While of interest, the Division does not consider this study to be adequate to support a conclusion that the levels of SP-B in Survanta are sub-threshold and not active and that the levels of SP-B in Infasurf are active.

In general, the in-vitro product differentiation protocols submitted by the sponsor appear adequately designed to address the "active moiety" approach referred to in the Division's May 24, 1996, letter. The Division continues to have concern, however, about the scientific rigor and validation of some of the methodology the sponsor plans to utilize in those studies and the sponsor's proposed plan for interpretation of the data. Pending receipt and review of the in-vitro product differentiation studies, the Division does not believe that the sponsor has provided adequate data to support their contention that SP-B is present in sub-threshold amounts in Survanta.

ONY also contends that the Division's analysis of the "same" drug issue for Infasurf and

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[13] Mizuno K, Ikegami M, Chen CM, Ueda T, Jobe A. Surfactant Protein-B Supplementation Improves In Vivo Function of Modified Natural Surfactant. Ped Res 37(3):271-276.

Survanta is inconsistent with the Agency's analysis of the "same" drug issue for Survanta and Exosurf in 1991. While current members of the Division were not involved in that determination and there are no clear records of the analysis applied at the time, the Division believes its analysis of the Infasurf and Survanta "same" drug question is entirely consistent with prior Agency action which determined that Survanta and Exosurf were different drugs for the purposes of the orphan drug regulations[14]. Exosurf is a synthetic mixture of DPPC, cetyl alcholol and tyloxapol that demonstrates surfactant activity in-vitro and in-vivo. The three components that make up the active surfactant mixture in Exosurf include two components not present in natural surfactant or in Survanta; These differences clearly meet the standard of "present and active in one surfactant and....either not present or present at levels that are inactive in the other surfactant" as described to ONY in the Division's May 24, 1996, letter. Similarly, the Agency has never raised any concerns that Infasurf and Exosurf are the "same" drug even though the orphan drug exclusivity for Exosurf had not expired when the Infasurf NDA was originally submitted. Finally, the Division has applied the same analysis to Curosurf, a porcine derived surfactant currently under review, and has determined that Curosurf is the "same" drug as Survanta under the orphan drug regulations.

Clinical comparison of Infasurf and Survanta

While ONY contends that they have provided adequate data to support a conclusion that Infasurf is not the "same" drug as Survanta, they also contend that they have provided adequate data to support a conclusion that Infasurf is clinically superior to Survanta, the second mechanism for "breaking" orphan drug exclusivity. In support of this claim the sponsor submitted the results of one trial directly comparing Infasurf and Survanta.[15]

The sponsor's original basis for the clinical superiority claim was the fact that in the RDS treatment trial, Infasurf treated patients achieved a statistically significant lower mean fraction of inspired oxygen content (FiO_2) and mean airway pressure (MAP) than Survanta treated patients for the first 24 hours of treatment. After 24 hours in the treatment trial, and throughout the prophylaxis trial, there were no significant differences between the treatment arms. The sponsor also claimed that Infasurf treated babies required fewer doses of surfactant and that the interval between doses was significantly longer than in Survanta treated patients.

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[14] Exosurf was approved as an orphan drug for the prophylaxis and treatment of RDS in neonates in 1990 and was granted 7 years of oprhan drug exclusivity. Survanta was approved in 1991 and was considered a different drug under the orphan drug regulations from Exosurf and was granted 7 years of orphan drug exclusivity.

[15] Study ISCT-92 compared Infasurf and Survanta 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. While this study was conducted under one protocol, it was analyzed as two separate studies with different post hoc defined primary endpoints.

The Division and Office do not concur with the sponsor's assertion that these findings are evidence of clinical superiority of Infasurf for several reasons, including: 1) the statistically significant findings were limited to physiologic parameters (e.g., FiO_2 and MAP) and the overall distribution of the number of doses received; there were no statistically significant findings for any clinically relevant outcomes such as mortality, air leaks, incidence of respiratory distress syndrome, or bronchopulmonary dysplasia; 2) the absolute magnitude of the mean differences observed between Infasurf and Survanta for FiO_2 (5%) and MAP (0.6 cm H_2O) were small and of questionable clinical relevance; the sponsor has been unable to provide any data to support the clinical relevance of such small differences; 3) the differences between Infasurf and Survanta for FiO_2 and MAP were only observed during the first 24 hours of therapy in the treatment trial; at 48 and 72 hours of therapy there were no statistically significant differences between the two surfactants (to address our concern in this area, Dr. Egan subsequently calculated the AUC of the first 72 hours of treatment and claimed that Infasurf was statistically significantly lower for both FiO_2 and MAP than Survanta; this recalculation did not provide any new information since the differences observed in the AUC over the first 72 hours simply represents another way of displaying the data and the observed differences are largely driven by the differences at 24 hours); 4) the sponsor's claims of "superiority" of Infasurf over Survanta are based on post hoc selection of two of the numerous secondary endpoints that were evaluated in the study with no statistical correction applied for multiple endpoints; 5) the observations for FiO_2 and MAP were limited to the treatment trial; in the prophylaxis trial there were no statistically significant differences on these or other endpoints; and 6) on clinically relevant endpoints such as mortality, air leaks, incidence of RDS and BPD, there were no statstically significant observations in favor of Infasurf over Survanta, and in fact, in the prophylaxis trial, there was a statistically significant difference on overall mortality in favor of Survanta over Infasurf.

Dr. Egan argues that the Infasurf versus Survanta trials were not designed or powered to demonstrate statistically significant differences between the two surfactants for the clinical endpoints. He further argues that the mortality finding in the prophylaxis trial should be disregarded since he believes it was caused by an "unexpectedly low" mortality rate in a subset of very low birth weight infants treated with Survanta. A post hoc subset analysis conducted by the sponsor that excluded the very low birth weight infants showed no statistically significant differences between the two surfactants. While it is true that these trials were not powered to demonstrate differences on clinical endpoints, the observation that the numerical differences between the two surfactants do not demonstrate a consistent advantage of Infasurf over Survanta suggest that the lack of statistically significant findings is not simply related to inadequate power. It is also inappropriate to dismiss a statistically significant finding on a clinical endpoint of considerable relevance, i.e., mortality in the prophylaxis trial, while at the same time placing great emphasis on two isolated statistically significant differences observed from a long list of secondary endpoints of less obvious clinical relevance.

In response to the Division concerns noted above, the sponsor submitted a further reanalysis of the Infasurf versus Survanta trials in which he created a post hoc defintion of severe RDS. This

reanalysis found that statistically significantly more infants in the Survanta group met the defintion of severe RDS than in the Infasurf group. Furthermore, the sponsor analyzed the ventilatory parameters of the patients that died or developed air leaks and found that this group as a whole had higher mean FiO_2 and MAP than the group that did not die or develop an air leak. The sponsor argues that this observation confirms his claim that ventilatory parameters are important predictors of outcome and provides support for the clinical relevance of early mean differences in FiO_2 and MAP between the Infasurf and Survanta groups.

The Division does not consider these findings adequate to support a claim of Infasurf superiority over Survanta since they are predicated on post hoc analyses and do not directly address the clinical significance of the small mean differences in ventilatory parameters observed in the treatment trial. Furthermore, the Division and the Center have a long history of not accepting physiologic variables (e.g., FiO_2, P_aO_2, and MAP) as endpoints, even when pre-defined, for approval decisions or decisions regarding comparative claims in diseases like RDS (e.g., ARDS, PPHN, and sepsis). The reason for this position is that for most physiologic variables it is difficult, or impossible, to interpret small mean changes between treatment groups, as such changes have not been correlated with clinically significant outcomes. The Division and the Center have seen many cases where promising findings on physiologic parameters, such as FiO_2 and MAP, have not been substantiated as being clinically meaningful when the appropriate trial using clinical outcomes have been conducted.

For the reasons outlined above, the Division and Office do not concur with the sponsor's assertion that Infasurf is clinically superior to Survanta.

MEMORANDUM

DATE: July 2, 1997 /S/ 7/2/97

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

THROUGH: James Bilstad, M.D.
Director, Office of Drug Evaluation II, HFD-10 /S/ 7/3/97

TO: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research, HFD-1

Murray Lumpkin, M.D.
Deputy Director (Review Management), Center for Drug Evaluation and Research, HFD-2

SUBJECT: Addendum to April 22, 1997, memorandum regarding the request by ONY for dispute resolution under 21 CFR 314.103 related to NDA 20-521

On March 14, 1997, ONY Inc., the sponsor of NDA 20-521 for Infasurf (calfactant), submitted a request for dispute resolution to the Office of the Center Director. The issues in question are whether Infasurf is the "same drug" as Survanta (beractant) under the Orphan Drug regulations and whether Infasurf is clinically superior to Survanta. In a memorandum dated April 22, 1997, the Division and the Office of Drug Evaluation II detailed their positions on the complex scientific and regulatory issues related to the Orphan Drug issues and the Infasurf application. The purpose of this memorandum is to update the previous memorandum to cover events and submissions that have occurred since the April 22, 1997, memorandum.

BACKGROUND

Regulatory History of NDA 20-521 (see the attached Administrative Review of and NDA 20-521, updated as of June 24, 1997)

Please refer to the April 22, 1997, memorandum for a detailed review of the regulatory history of NDA 21-521 to that time. This document will update the regulatory history only as it relates to the "same" versus "different" drug issues (i.e., submissions, meetings, agreements, etc. related to NDA review issues other than the same vs different drug issue will not be discussed).

On April 10, 1997, Dr. Lawrence Olanoff, M.D., Ph.D., Vice President, Scientific Affairs, Forest Laboratories (Forest is a partner of ONY for NDA 20-521) spoke with Dr. Murray Lumpkin by phone to discuss the status of the Infasurf application. Dr. Olanoff subsequently submitted a letter to Dr. Lumpkin on April 14, 1997 in which he outlined the sponsor's assertion that they

had submitted adequate data to demonstrate that Infasurf and Survanta are not the "same" drug and that Infasurf is clinically superior to Survanta. Dr. Olanoff suggested that the Agency employ outside experts in surfactant chemistry and neonatology to review the data submitted by ONY and requested that ONY be given the opportunity to present data to the outside experts before the experts and the Agency reached any conclusions regarding the Infasurf application.

On May 7, 1997, a Tentative Approval letter was issued to ONY for NDA 20-521. The letter stated that NDA 20-521 could not receive final approval pending expiration of the Orphan Drug exclusivity for Survanta.[1] In response to the letter, Dr. Egan sent a letter to Dr. Bilstad dated May 13, 1997, in which he argued that the package insert included by FDA with the tentative approval letter in fact supported ONY's position that Infasurf is not the "same" drug as Survanta and that Infasurf is clinically superior to Survanta and, therefore, Infasurf should be immediately approved (see detailed analysis of the contents of this letter below).

On May 28, 1997, ONY submitted the preliminary results of the SP-B portion of their in-vitro protocol designed to demonstrate that Infasurf and Survanta are not the "same" drug by the approach referenced in the Division's letter of May 24, 1996.[2] Also on May 28, 1997, a meeting at the Center level was held to discuss the sponsor's appeal to Dr. Woodcock on the Orphan Drug issue.[3] At that meeting, the Division reviewed the issues raised by ONY in their March 14, 1997, appeal letter to Dr. Woodcock. These issues were discussed by the group and the overall consensus of the meeting was general agreement with the position developed by the Division. However, it was decided that ONY would be given the opportunity to present their case to Drs. Woodcock and Lumpkin in a subsequent meeting before a final Center determination was made and a response to the March 14, 1997, appeal letter was issued.

One June 9, 1997, Dr. Egan sent a letter to Mr. Morrison, the CDER Ombudsman, in which he again outlined ONY's belief that they have adequately demonstrated that Infasurf and Survanta are not the "same" drug and that Infasurf is clinically superior to Survanta, or at the very least

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[1] The Tentative Approval letter stated: "Due to the orphan exclusivity granted to Ross Laboratories' product Survanta, your application for Infasurf may not be finally approved for marketing under Section 505 of the FFDCA until July 1, 1998, unless you can show that Infasurf and Survanta should not be considered the "same drug" within the meaning of the Orphan Drug regulations, 21 CFR Part 316."

[3] Attendees at the May 28, 1997, meeting included Drs. Woodcock, Lumpkin, Williams, Bilstad, Jenkins, McCormick, Chiu, Ms. Dickinson, and Mr. Morrison.

provides a "major contribution to patient care" as defined under the Orphan Drug regulations.[4] Dr. Egan attached to the letter a "detailed analysis" of these issues for the Agency's review. The analysis paper attached to the June 9, 1997, letter closely parallels the presentation made by the sponsor at the June 11, 1997, meeting with the Center and will serve as the primary framework for the Division's response to the issues raised by ONY (see below). On June 11, 1997, ONY met with the Center.[5] Dr. Egan, Mr. Kaplan (ONY's legal counsel), and Drs. Notter, Holm, and Asau (ONY's expert consultants) presented their analysis of the issues to Drs. Woodcock and Lumpkin. A question, answer, and discussion session followed the sponsor's presentation. At the conclusion of the meeting, the sponsor was told that the Center would carefully consider their arguments and get back to them with a response to their appeal request in a timely manner.

DIVISION POSITION ON ORPHAN DRUG ISSUES

Please refer to the April 22, 1997, memorandum for a detailed analysis of the Division's position on the "same" vs "different" drug issue and on the clinical comparison of Infasurf and Survanta. The following analysis will provide the Division's perspective on the issues raised by ONY in the May 13, 1997, letter to Dr. Bilstad, the June 9, 1997, letter to Mr. Morrison, including the attached sponsor's analysis of the issues, and at the June 11, 1997, meeting between ONY and the Center.

<u>May 13, 1997, Letter to Dr. Bilstad</u>

In this letter the sponsor stated three ways in which, in their view, the package insert included with the May 7, 1997, tentative approval letter for NDA 20-521 demonstrated that Infasurf and Survanta were not the "same" drug as defined under the Orphan Drug Regulations. Each of these issues will be addressed separately:

1. *Activity of SP-B and SP-C in Survanta and Infasurf*

   The sponsor states that the FDA has determined that the proteins SP-B and SP-C have not been shown to be active components in Survanta and are active components of Infasurf. In support of this claim, the sponsor outlines two lines of evidence;

   a. The sponsor claims that during its review of the Survanta NDA the "Agency decided that the study Laboratories submitted had not demonstrated that the proteins in Survanta were active" with reference to FDA Chemist's Review #4, February 24, 1991. A review of the NDA file for Survanta (NDA 20-032) reveals that in a FAX sent to Ross Laboratories by the Division of Oncology and

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[4] One of the definitions of clinically superior includes 21 CFR 316.3(b)(3)(iii) which states: "In unusual cases, where neither greater safety nor greater effectiveness have been shown, a demonstration that the drug otherwise makes a major contribution to patient care."

[5] FDA attendees included Drs. Woodcock, Lumpkin, Bilstad, Jenkins, McCormick, Ms. Dickinson, and Mr. Morrison.

Pulmonary Drug Products on December 19, 1990, the following comment from Chemist's Review #3 was included: "The 'Description' section of the package insert should be revised to delete the sentences that make reference to proteins SP-B, SP-C, and unless of course, data are provided that demonstrate that these proteins retain their activity

In an amendment to NDA 20-032 dated January 24, 1991, Ross Laboratories submitted a report titled " 60386X (Survanta), The Presence and Activity of Surfactant Associated Proteins", which they stated "provides data to demonstrate the role of the proteins in the activity of Survanta."[6] One important component of this report was a comparison of Survanta versus various mixtures of lipids in in-vitro assays of surfactant activity. These assays demonstrated that Survanta was more active than a complex mixture of lipids that closely paralleled the major lipid composition of Survanta, but contained no surfactant-associated proteins (i.e., Lipid Mix C: DPPC, PC,). The chemistry reviewer, Dr. Theodorakis, reviewed these data and concluded "it does not unequivocally prove that the traces of protein in the surfactant

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the cause of the better performance of the surfactant. For instance, the Lipid Mix C does not contain all the different lipids that exist in minor concentrations in BLL (bovine lung lipids).... With this in mind one should wonder whether the poor performance of Lipid Mix C in comparison to Survanta is due to the presence in the latter of traces of proteins SP-B and SP-C or of all the different lipids that are present in small concentrations in BLL (bovine lung lipids), or for that matter in the presence of both."

Analysis: In 1991, Abbott was of the opinion that the surfactant associated proteins (SP-B and SP-C) present in Survanta were active and necessary for the overall activity of Survanta. To this end they conducted various experiments and submitted them to the Agency. While, as Dr. Theodorakis pointed out at the time, these studies did not definitively prove that the surfactant-associated proteins in Survanta were active, they certainly provided substantial support of position. This position is further strengthened by two additional pieces of

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[6] In this report, Ross provided the following lines of evidence that SP-B and SP-C were active in Survanta (taken from their introduction); 1) evidence indicating the presence of specific surfactant-associated proteins in organic solvent extracts of lung material and in the finished product (i.e., Survanta), 2) documentation of the inability of even complex multi component lipid admixtures containing no protein to simulate the characteristics of natural lung surfactant, thereby indicating the "necessity" of the protein content, 3) evidence indicating the role and nature of the effect of the proteins when included in simple or complex lipid admixtures, 4) evidence indicating the effect of heat treatment on complex lipid admixtures alone versus the effect of identical heat treatment on complex lipid admixtures containing surfactant associated protein, and 5) discussion of the extraordinary organic solvent and thermal stability of the SP-B and SP-C surfactant associated proteins.

evidence; 1) In 1982, Fujiwara, one of the Japanese inventors of Survanta, described a series of experiments in which bovine lung lipids (BLL), the lung extract that serves as the base for production of Survanta

Their experiments demonstrated that the BLL themselves were surface active and that the protein-phospholipid fraction of BLL was essential for the full reproduction of the original surface properties in experiments where the surface activities of the various fractions and combinations of fractions were assayed; and 2) The preliminary data submitted by ONY on May 28, 1997, from their in-vitro experiments designed to show that Infasurf and Survanta are "different" based on the SP-B "active moiety" approach, demonstrated that when Survanta had 80% of its usual protein content removed, its surface activity and biologic activity were reduced.

These additional lines of evidence, combined with the data generated by Ross Laboratories, provide very strong support to the argument that the surfactant-associated proteins in Survanta are active. Unfortunately, none of these experiments are adequate to address the question of whether it is the SP-B, SP-C, or both in Survanta that are contributing to its activity. Even though the majority of protein in Survanta is SP-C, it is impossible to state, based on available data, that the SP-B in Survanta is not active. It is also a misrepresentation on the part of the sponsor to state that Dr. Theodorakis' comment in chemistry review #4 for NDA 20-032 demonstrates that the Agency had determined that the proteins in Survanta were not active. To the contrary, the statements that Dr. Theodorakis had suggested be deleted from the Survanta package insert regarding SP-B and SP-C, unless data were provided demonstrating that the proteins were indeed active, were retained and appear in the FDA approved package insert.

b. Package insert descriptions reflect differences in protein activity
In support of this argument, the sponsor contends that the package insert descriptions of Infasurf and Survanta reflect the Agency's differential determinations of protein activity. They state that Survanta has no specified amount of total protein or SP-B, only a maximum allowable total protein, <1.0 mg/mL, which means it could, in fact, have none. In contrast, the state that Infasurf has a specified amount of total protein, 0.65 mg/mL, and of SP-B, 0.26

[7] Tanaka Y, Takei T, Kanazawa Y, Seida K, Masuda K, Kiuchi A, Fujiwara T. Preparation of surfactant from minced bovine lung: chemical composition and surface properties. J Jap Med Soc Biol Interface, 1982; 13:87-94.

mg/mL.[8]

Analysis: Both labels include reference to SP-B and SP-C in the description section along with other important components of the surfactant. The sponsor's claim that Survanta only has a maximum allowable level for protein and, in fact, could have no protein is incorrect. The actual release specifications for Survanta (to which ONY would not be expected to have access) include a specification for total protein Thus, there are both upper and lower limits on the amount of total protein and a batch of Survanta , total protein would not be released. ONY has not produced any evidence in support of their claim that Survanta could in fact have no protein and, to the contrary, have actually submitted data from their own analyses of Survanta which demonstrate the total protein content to be within the stated specifications for release. With regard to the lack of a stated value for the amount of SP-B in Survanta, the sponsor has failed to acknowledge that until ONY developed and validated an , there was no validated method to quantitate SP-B in surfactants. In fact, in the original submission of NDA 20-521 ONY did not propose rather they only proposed a specification for total protein. ONY committed to develop and validate as part of the resubmission of NDA 20-521 in July 1995. This validated was needed to support ONY's claims that SP-B levels in Infasurf were much higher than those in Survanta.

In summary, both package inserts list SP-B and SP-C in the description sections and ONY's contentions that Survanta could in fact have no protein is incorrect. The fact that ONY now has a specification for the amount of SP-B in Infasurf while Survanta does not, does not demonstrate that the two products are different. It simply demonstrates the advance in assay methodology that has occurred since

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[8] The description section of the Survanta package insert states: "It is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate (dipalmitolyphosphatidylcholine), palmitic acid, and tripalmitin are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant. The resulting composition provides 25 mg/mL phospholipids (including 11.0-15.5 mg/mL disaturated phosphatidylcholine), 0.5-1.75 mg/mL triglycerides, 1.4-3.5 mg/mL free fatty acids, and less than 1.0 mg/mL protein. Its protein content consists of two hydrophobic, low molecular weight, surfactant associated proteins commonly known as SP-B and SP-C. It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A." The description section of the Infasurf package insert states: "It is an extract of natural surfactant from calf lungs which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C).....Each mL of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg proteins including 0.26 mg of SP-B."

the Survanta application was approved in 1991.

2. *Different established names for Infasurf and Survanta*
The sponsor states that the decision of United States Adopted Names Council (USAN) to assign different established names to Infasurf (i.e., calfactant) and Survanta (i.e., beractant) and the acceptance of these names by FDA proves they are "different" since if they were the "same" drug they would have the same name, "in much the same manner as ANDAs carry the same established name as the reference drug."

Analysis: This line of reasoning fails to recognize the different standards that are applied to the assignment of names by USAN and determination of "sameness" under the Orphan Drug regulations. The Orphan Drug regulations acknowledge that two products can in fact have chemical differences (e.g., different amino acid sequences of proteins that may result in assignment of different USAN names) and still be considered the "same drug" for purposes of orphan drug exclusivity. The assignment of names by USAN to complex biologic mixtures, such as surfactants, is totally unrelated to the NDA/ANDA paradigm of generic and innovator reference listed drugs and wholly separate from the determination of "sameness" under the Orphan Drug regulations.

3. *Acute Clinical Effect section of Infasurf labeling*
The sponsor states that the "Acute Clinical Effects" paragraph in the Clinical Trials section of the Infasurf labeling falls under a section headed "Infasurf versus Survanta".[9] The sponsor further states that since all the controlled clinical trials of Infasurf included either Exosurf or Survanta as active controls, this paragraph implies that these acute clinical effects were in comparison to the other active surfactants. The sponsor, therefore, contends that these acute clinical advantages of Infasurf over Survanta meet the Orphan Drug regulation definition of clinical superiority.

Analysis: This argument again represents an incorrect interpretation of the package insert language. While it is true that the physical location of the "Acute Clinical Effects" paragraph appears to be under the section of the labeling describing the "Infasurf versus Survanta" comparison trial, this paragraph in fact is based on an analysis of all the controlled clinical trials, not just the Infasurf versus Survanta trial. The physical location of the paragraph under the "Infasurf vs Survanta" heading was an editing oversight on the part of the Division. The sponsor's claim that the acute clinical effects statement is evidence of superiority of Infasurf over Survanta is incorrect. The reference is actually to the change in these parameters from baseline in the Infasurf-treated patients rather than a comparison of the effects of Infasurf and Survanta. In fact, very similar statements

[9] The paragraph 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 (FiO_2) and mean airway pressure (MAP) during the first 24 to 48 hours following initiation of Infasurf therapy."

regarding acute physiologic changes that may occur after administration of surfactant are also included in the package inserts of Exosurf and Survanta. These statements are included to make the physician aware of the rapid changes in lung physiology which can occur following the administration of any effective surfactant in infants with RDS and the need to be ready to rapidly adjust FiO_2 and ventilator pressure to avoid serious potential toxicity (e.g., barotrauma).

June 9, 1997, Letter from Dr. Egan to Mr. Morrison

The text of this letter does not contain any new data or arguments and will not be specifically addressed. The sponsor did attach to this letter a "detailed analysis" of the issues entitled "Explaining how clinical studies and differences in the active moieties of Infasurf and Survanta demonstrate that they are not the 'same drug'." A copy of this monograph is attached to this memorandum and is analyzed in detail below, from the Division's perspective (note: the headings used below will parallel those in the sponsor's document).

A. "Point for Resolution"
This section is only a summary of the issues in dispute and requires no analysis.

B. "History of Scientific Dispute"
This section lists a summary of the sponsor's interpretation of the events that have transpired since the original submission of NDA 20-521. Please refer to the attached "Administrative Review of and NDA 20-521: Infasurf (calf lung surfactant)" for a more detailed summary of the history of these applications. Only issues raised by the sponsor that are factually inaccurate or need further explanation by the Division will be commented on below.

4. Following the July 6, 1995, meeting with the sponsor, the Division sent a letter to ONY on July 13, 1995, which stated that the data and arguments presented by the sponsor provided a "theoretically valid" argument that Infasurf and Survanta are different.[10] The letter made clear that the

[10] The text of the letter stated: "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 SP-B to the effect of Infasurf must be submitted in a manner consistent with an NDA submission. 2.) Commit to provide from an FDA inspected laboratory for the analysis of SP-B 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 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

determination of whether Infasurf and Survanta were in fact different remained a review issue.

6. At an April 24, 1996, Center level meeting the "same vs different" drug issue was discussed and it was decided that, based on the currently available data, Infasurf and Survanta were the "same" drug for Orphan Drug exclusivity purposes. It was further decided that in order to prove that Infasurf is "different" from Survanta the sponsor must provide quantification of SP-B and proof that the level of SP-B in Survanta is inactive. This position recognized that quantitative differences in an "active" ingredient for two complex mixtures of "actives" was inadequate evidence to support a claim that the two products are "different", unless the "active" was not present in one product or the levels of the "active" in one product could be demonstrated to be so low as to be "inactive". The sponsor had been informed that a Center level meeting was scheduled to discuss this issue during a March 20, 1996, meeting with the Division. During that meeting the "same vs different" drug issue was discussed extensively and the sponsor was informed that the Division's position was that Infasurf and Survanta were the "same" and that quantitative differences in the amount of SP-B would be inadequate to demonstrate that Infasurf was "different" from Survanta. Thus the sponsor's assertion that they had not been made aware of the Division's position on this issue until April 26, 1996, is incorrect.

8. The letter from Ross Laboratories referenced by ONY was written by Michael Haney, Director, Regulatory Affairs to Marlene Haffner, Director, Office of Orphan Products Development, FDA, on July 22, 1996, with a copy directed to Dr. Jenkins. The letter was unsolicited and a response has not been issued by the Agency. The contents of this letter played no role in the Division's assessment of the Orphan Drug issues related to the Infasurf application and the Division has not consulted with Ross Laboratories on these issues during the two year history of NDA 20-521 for Infasurf.

12. ONY's November 22, 1996, letter was reviewed by the Division in consultation with Dr. Bilstad, the Office of General Counsel, the Office of Orphan Products, and representatives from CBER who were familiar with the Berlex case cited by ONY in their letter. ONY was informed during a December 9, 1996, teleconference by Dr. Himmel that the Division/Office

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the data requested in #1. above."

review of the data submitted by ONY had resulted in a determination that the data were inadequate to support a conclusion that Infasurf is clinically superior to Survanta. Contrary to the sponsor's statement, the Division did not rely only on data that was included in the study report of the Infasurf vs Survanta trial, the reviewers evaluated all the data and analyses submitted by ONY, solicited additional information from ONY regarding the Berlex case, and consulted with other Agency staff prior to reaching its decision.

15. At the February 26, 1997, meeting, the Division expressed its general agreement with the approach ONY was proposing for its in-vitro protocols, but stated that it could not agree to ONY's proposed plan for analyzing the study data due to the many remaining uncertainties regarding the methods to be used and the range of data that may be obtained (e.g., the sensitivity of the to detect differences will need to be evaluated in determining an appropriate definition of "equivalence"). The sponsor expressed their frustration that the Division could not "sign off" on the protocol. They were advised that the Division had provided comments on the protocol twice which focused on the general design issues and obvious areas of deficiencies. They were advised that a certain amount of risk in conducting the protocol had to be assumed by themselves and that the Division had already committed a great deal of its resources and time to the review of these protocols. They were informed that use of the Division's limited resources in this manner only served to delay the Division's efforts to review and resolve the other outstanding deficiencies for NDA 20-521.

18. The sponsor fails to note that at the February 26, 1997, Dr. Hudak, one of ONY expert consultants, stated that in his opinion Infasurf was clinically superior to Survanta; however, he also noted that he agreed with the Division that the data available from the Infasurf versus Survanta trial was inadequate to reach a conclusion that Infasurf was clinically superior to Survanta.

C. "Orphan Drug Act and Regulations"

The Division will not address this section of the sponsor's analysis in detail; rather we will defer to the Office of Orphan Products Development and the Office of General Counsel. We do note, however, that the last line the sponsor quotes from the January 19, 1991 FR notice states: "These proposed regulations attempt to ensure that improved therapies will always be marketable, and that orphan drug exclusive approval does not preclude significant improvements in treating rare diseases." In the Division's opinion, ONY has not provided adequate data to demonstrate that Infasurf represents a significant improvement over Survanta.

D. "Infasurf Should not be Considered the 'Same Drug' as Survanta"

1. Infasurf will make a "Major contribution to patient care"

Contrary to the sponsor's assertion, the Division has carefully reviewed and considered all the data and analyses that have been submitted by the sponsor in support of their claim that Infasurf is clinically superior to Survanta or that Infasurf "makes a major contribution to patient care" as described under the Orphan Drug regulations. The Division's analysis of the Infasurf versus Survanta trial is detailed in Dr. Jenkins' memorandum to Drs. Woodcock and Lumpkin dated April 22, 1997. As noted above, even one of the sponsor's expert consultants, Dr. Hudak, stated in the February 26, 1997, meeting that the data from the Infasurf versus Survanta trial were inadequate to make a determination of clinical superiority. The sponsor's analysis of this trial consistently downplays the observation that the mortality rate in the prophylaxis arm of the trial actually favored Survanta and that for the usual, well established clinical endpoints evaluated in the trial (e.g., mortality, air leaks, incidence of RDS or bronchopulmonary dysplasia), Infasurf was not superior to Survanta. The sponsor argues that the trial was not designed to show differences on these well established clinical endpoints and that a trial to demonstrate superiority of one surfactant over another on these endpoints would represent a significant burden to the company due to need for very large sample sizes. The sponsor's "lack of power" argument for clinically relevant endpoints is contrary to the mortality findings in the prophylaxis arm of the trial (i.e., significant differences in mortality favoring Survanta were observed) and cannot overcome the fact that the trial failed to show even numerical trends favoring Infasurf on the well established clinically relevant endpoints traditionally used to assess the effectiveness of surfactants in RDS. The "lack of power" argument also does not justify the use of endpoints whose clinical relevance (i.e., correlation with well established clinically relevant outcomes such as mortality) have not been adequately established.

The sponsor's primary focus for their claim of clinical superiority is on physiologic endpoints, such as FiO_2 and MAP, where small, statistically significant (Note: none of the sponsor's statistical analyses included adjustments for multiple comparisons), mean differences favoring Infasurf, primarily during the first 24 hours following initiation of therapy, were observed. The sponsor acknowledges that these mean changes were small and of questionable significance. To further explore these differences, the sponsor conducted a post hoc analysis to determine the number of infants who had severe, persistent or progressive respiratory failure (i.e., FiO_2 >60% and >10 cm H_2O MAP from 0-72 hours) despite surfactant therapy. This post hoc analysis found that 4% of Infasurf-

treated patients and 11% of Survanta-treated patients had severe, persistent respiratory failure (the sponsor argues that these findings are "statistically significant", however it is invalid to apply hypothesis testing procedures to such post hoc exploratory analyses). The sponsor then argues that since the mortality rate in the group of patients with severe, persistent respiratory failure in the trial was 88%, that "most infants with this severe, persistent RDS today would achieve a 'major contribution' to their care if they had access to treatment with Infasurf rather than only Survanta." The Division considers this post hoc analysis of severe respiratory failure to be useful for hypothesis generation, but invalid to reach a conclusion that the observed difference in the rate of severe RDS represents a true difference. Furthermore, the sponsor has absolutely no data from which to reach the conclusion that infants who develop severe RDS on Survanta would fare better if they were treated with Infasurf. This represents speculation on their part, perhaps based on anecdotal, uncontrolled clinical experience. In the Infasurf versus Survanta controlled trial, equal numbers of Infasurf-treated and Survanta-treated patients crossed over to the other surfactant as allowed by the protocol. This observation is counter to the sponsor's position that Infasurf is clinically superior to Survanta.

In summary, the Division has carefully reviewed all the data and analyses presented by the sponsor in support of the alleged clinical superiority of Infasurf. We continue to believe that the available data do not support a conclusion that Infasurf is clinically superior to Survanta or that Infasurf offers a "major contribution to patient care" that is not currently available by use of Survanta. The sponsor appears to conclude that since the Division does not agree with their interpretation of the data that the Division has not carefully considered all the data and analyses. On the contrary, the Division has committed a significant amount of time and resources to reviewing these issues and has consistently sought the advise and counsel from others within the Agency in evaluating the complex scientific and regulatory issues raised by the Infasurf application.

2. Orphan Drug Rules for Macromolecules Were Not Intended, and Are Not Appropriate for Lung Surfactants

The sponsor argues that naturally derived surfactants should not be considered under the "macromolecule" standards listed in the Orphan Drug regulations, including the regulations at 21 CFR 316.3(b)(13)(ii)(D) for "closely related, complex, partly definable drugs", for several reasons, including; 1) the vast majority of the composition of naturally derived surfactants are in fact "small" molecules; 2) the standards developed under the Orphan Drug regulations for macromolecules deal exclusively with issues of micro heterogeneity within macromolecules that are the active

moiety of drugs, not issues of heterogeneity among molecules in complex mixtures of drugs or biologics; 3) the example given under 21 CFR 316.3(b)(13)(ii)(D) of a "closely related, complex, partly definable drug", i.e., a live viral vaccine, is not applicable to naturally derived lung surfactants (the sponsor notes that despite the fact there were several naturally derived lung surfactants with Orphan designation at the time the Orphan Drug regulations were finalized in 1991, no mention was made of surfactants in the regulations), and 4) the sponsor argues that the Agency's response to a comment (i.e., #21) in the preamble to the final Orphan Drug regulations demonstrates the Agency's intent to evaluate differences other than micro heterogeneity between macromolecular drugs using the same precess it had historically used for "small" molecule drugs.

Many of the issues raised by the sponsor in this section will require further review and comment by the Office of Organ Product Development and the Office of General Counsel. The Division agrees with ONY that the final Orphan Drug regulations do not specifically identify a regulatory mechanism for determining that a drug is the "same" as a previously approved drug for drugs like Infasurf and Survanta which are comprised of complex mixtures of both large and small molecules. It is the Division's position that the most appropriate analysis to apply to naturally derived surfactants is analogous to the analysis applied in 21 CFR 316.3(b)(13)(ii)(D) since Infasurf and Survanta are complex, partly definable mixtures of small (i.e., lipids) and large molecules (i.e., proteins) with similar therapeutic intent. Since Infasurf and Survanta have very similar qualitative compositions of "active" components, albeit significant differences in quantitative content of certain "active" components, the Division believes that such complex mixtures should be considered the "same" and that the burden of proof under the Orphan Drug regulations is on the sponsor to demonstrate the clinical superiority of the second product. The Division believes that this approach adheres to the intent of the Orphan Drug regulations as best defined by the reference in 21 CFR 316.3(b)(13)(ii)(D) to "closely related, complex, partly definable drugs."

3. The Agency Has Set a Precedent by Approving Two Orphan Lung Surfactants Which both Contain Macromolecules (Survanta and Exosurf) on Compositional Differences

The sponsor contends that the approval of Survanta in 1991, despite the Orphan Drug exclusivity granted to Exosurf on its approval in 1990, is inconsistent with the Agency's current approach to Infasurf and Survanta. While members of the current Division were not involved in that determination and there are no clear records of the analysis applied at that time, the Division has reviewed the available information on both products

and disagrees with the sponsor's analysis. The Division's analysis of the Infasurf vs Survanta case is entirely consistent with prior Agency action which determined that Survanta and Exosurf were "different" drugs for the purposes of Orphan Drug exclusivity. Exosurf is a synthetic mixture that demonstrates surfactant activity in-vitro and in-vivo. The three components that make up the active surfactant mixture in Exosurf include two components not present in natural surfactant or in Survanta; These differences clearly meet the standard of the "active moiety" approach as described to ONY in the Division's letter of May 24, 1996; i.e., "present and active in one surfactant and....either not present or present at levels that are inactive in the other surfactant." Similarly, the Agency has never raised any concerns that Infasurf and Exosurf are the "same" drug even though the orphan drug exclusivity for Exosurf had not expired when the Infasurf NDA was originally submitted.

4. <u>"Principal Structural Features" of Exosurf, Survanta, and Infasurf are different</u>

The sponsor contends that the principal structural features of the three surfactants, particularly their macromolecular components, are different and that this fact has been acknowledged by the Agency's own reviews of the products. As noted above, this argument is based on the sponsor's contention that the Agency determined at the time of the approval of Survanta that the protein fraction (SP-B and SP-C) was inactive. This is a misinterpretation of the Agency's action and is inconsistent with the description section of the Survanta package insert; i.e., SP-B and SP-C are specifically mentioned in the section that describes the various components of Survanta. The sponsor further contends that the report by Mizuno et al in 1995 demonstrates that the level of SP-B is subthreshold and inactive.[11] Please see the Division's discussion of this manuscript in the April 22, 1997, memorandum from Dr. Jenkins to Drs. Woodcock and Lumpkin. This study demonstrated that supplementation of Survanta with 2% SP-B improved its surface active properties in pre-term rabbits. The study authors concluded that "These results demonstrate that there is insufficient SP-B in Survanta for <u>optimal function</u> (underline added) immediately after treatment." The author's conclusion was not that SP-B in Survanta was inactive, only that the level was insufficient for "optimal" function. The author's do state parenthetically that "in-vivo function of lipid-extracted Survanta was not different from that of Survanta (data not

[11] Mizuno K, Ikegami M, Chen C, Ueda T, Jobe AH. Surfactant protein-B supplementation improves in-vivo function of a modified natural surfactant. Pediatr Res 1995; 37:271-276.

shown)." If one assumes that the "lipid-extracted" Survanta preparation was protein-free, this finding (again remembering that the authors did not describe the methods of preparation or the methods of analysis of the modified Survanta or provide any data from their experiments with this modified Survanta preparation) would appear to support ONY's position that the protein fraction of Survanta is inactive. However, ONY's own experiments with partially de-proteinated Survanta and the work of the inventors of Survanta (see above) have clearly demonstrated that the protein fraction of Survanta is active. In summary, the Mizuno paper, while interesting, does not provide any data on which to base a judgement that the SP-B fraction of Survanta is inactive.

5. <u>The "Active Moiety" Methodology is Appropriate for Lung Surfactant Evaluation</u>

The sponsor argues that the "active moiety" of Infasurf is different from that of Survanta and in support of this assertion refers to various different in-vitro and preclinical in-vivo physiologic and pharmacologic activities of the two surfactants (i.e., surface activity, adsorption, resistance to inhibition, potency, activity in ex-vivo surfactant deficient lungs, activity in animal models of surfactant deficiency). While it is true in many cases that two drugs with different active moieties are very likely to have different physiologic/pharmacologic properties, it is also true that two drug products with the same active moiety may also have different physiologic/pharmacologic properties; i.e., as might occur with two drug products that contain the same active moiety in a different dose or in formulations with different bioavailabilities. The physiologic/pharmacologic properties of a drug product are not adequate surrogates for the active moiety of the drug product, a point the sponsor repeatedly appears to fail to recognize in their arguments as to why Infasurf and Survanta should not be considered the "same" drug. The sponsor also argues that Infasurf is not a modification of Survanta and states that, in fact, Infasurf received Orphan Drug designation before Survanta. This point and the rest of the argument offered by ONY in this section is irrelevant to the determination of "sameness" under the Orphan Drug statutes; what matters is which surfactant gains approval and Orphan Drug exclusivity first and whether the second product is "different" or clinically superior to the first. As noted above, the Division considers Infasurf to be the "same" as Survanta for Orphan Drug exclusivity purposes and does not believe that the sponsor has demonstrated that Infasurf is clinically superior to Survanta.

5. <u>The Rationale for Comparison of Survanta and Infasurf Must be Grounded in the Substance and Intent of the Regulations</u>

This section essentially restates earlier positions that the regulatory framework established for macromolecular drugs under the Orphan Drug regulations should not apply to Infasurf due to the lack of issues related to micromolecular heterogeneity for the Infasurf versus Survanta comparison; i.e., the Agency should apply the "small" molecule framework to the analysis of Infasurf. The sponsor argues that if the Orphan Drug regulations do not provide "same drug" methodology specifically tailored for certain types of drugs or biologics that the "small" molecule rules must be applied. The Division believes that its approach to the "same" drug determination for Infasurf is fully in line with the intent of the Orphan Drug Act and regulations and historically consistent with the Exosurf versus Survanta precedent.

E. "Studies to Demonstrate Infasurf is Not the "Same Drug" as Survanta"
In this section the sponsor claims that after initially suggesting that ONY need only test for content differences in SP-C in Infasurf and Survanta, the Agency later changed this to a requirement to "dismantle" and "reassemble" both drugs to determine "activity" of the components. The sponsor further states that the Agency has been unable and unwilling to agree to a technically feasible study protocol to accomplish this goal. The sponsor notes that their attempts to determine the activity of SP-B and SP-C were unsuccessful due to technical difficulties.

It is inaccurate for the sponsor to assert that they were told by the Division that all that was needed to establish that Infasurf and Survanta are "different" was to in the two products. The attached Administrative Review of the NDA files clearly demonstrates that was only one component of the burden on the sponsor to prove that the surfactants were not the "same". As the Division and the Agency reviewed the issues and the data submitted by the sponsor over the first several months of the NDA review, it became clear that simply establishing quantitative differences in the levels of SP-B between the two surfactants would not be adequate to demonstrate that they were "different"; rather it would be necessary to demonstrate the significance of any observed quantitative differences. This is a logical, scientifically valid conclusion consistent with the intent of the Orphan Drug regulations; i.e., two drug products that contain the same active moiety at different doses would be considered to be the "same". This approach is embodied in the "active moiety" approach which was agreed upon at the April 24, 1996, Center meeting on this issue and which was communicated to ONY in a teleconference on April 26, 1996, with a follow-up letter from the Division to ONY dated May 24, 1996.

It is also inaccurate for the sponsor to assert that the Division has been unable or unwilling to agree to a technically feasible in-vitro study protocol to address the

"active moiety" approach. The Division has spent considerable amounts of time and resources reviewing various iterations of ONY's proposed protocol. This review involved medical officers, chemists, statisticians, representatives from the Office of Orphan Drug Development, and Dr. Bilstad. On three separate occasions the Division provided ONY with comments on their proposed protocols. In addition, the Division met with ONY on February 26, 1997, to discuss the in-vitro protocols and the Division's remaining concerns. This level of effort far exceeds the amount of time and resources the Division normally devotes to review of even pivotal, Phase 3 study protocols. At the February 26, 1997, ONY was seeking Division "sign-off" on the protocol. The Division clearly stated the reasons it could not provide such assurances of the acceptability of the protocol at that meeting, including the lack of details regarding the methods to be used to fractionate the surfactants, concerns about the sensitivity of the proposed assays of activity, and the sponsor's broad definitions of "equivalence." The sponsor was advised of the need to make the studies as scientifically rigorous as possible in order to allow them to serve as the basis for regulatory decision making. It is noteworthy that the sponsor encountered just the type of technical difficulties that the Division was concerned about in their attempts to conduct the in-vitro protocol.

June 11, 1997, Meeting between ONY and Center

Many of the issues raised by the sponsor at the June 11, 1997, meeting have already been addressed in this memorandum or in the April 22, 1997, memorandum. Based on a review of the sponsor's overheads presented at the meeting, a transcript of the recording of the meeting provided by Mr. Kaplan, and Dr. Jenkins' memory and notes of the meeting, the following issues warrant further response from the Division.

A. "Active" Ingredients of Surfactants

The sponsor stated in the meeting that the "active" ingredients of the three relevant surfactant products

In fact, Survanta and Infasurf can be viewed as mixtures of these six "active" components (ignoring for the purposes of this argument the possibility that other recognized or unrecognized components in each product may also contribute to the product's activity) that differ only in the quantitative levels of certain of the components All six components are present in both products, however, data are lacking to allow a definitive determination as to the degree of contribution of a given component at the level it is present in each surfactant to the overall surface activity of the two surfactants.

The Division has taken the position that these products are closely related, complex, partly definable products with the same therapeutic intent and are, therefore, the "same" unless the sponsor can provide data to satisfy the "active moiety" approach (i.e., demonstrate that the levels of a component are inactive in one product and active in the other) or demonstrate that the second product is clinically superior to the first. In the Division's opinion, the sponsor has done neither. It is also worth noting that if the sponsor's preferred analysis of the "same" drug issue under the Orphan Drug regulations, i.e., the "small" molecule approach, is applied to Infasurf and Survanta, a conclusion that they are the "same" is reached since all of the six "active" components identified by the sponsor are present in both products.

B. Focus on pharmacologic activity rather than "active moiety"

Throughout the meeting the sponsor maintained that Infasurf and Survanta have different "active moieties" based on different in-vitro and preclinical in-vivo physical and pharmacologic activities. As noted above, while the active moiety is the part of the drug product that is responsible for its intended pharmacologic activity, pharmacologic activity is not a valid surrogate for the active moiety of a product. When pressed by Dr. Jenkins to define the "active moiety" of Infasurf and Survanta, Dr. Notter, expert consultant to ONY, listed the "active" ingredients noted above. Dr. Jenkins pointed out that this approach to defining the active moiety for surfactants is very different to that taken by ONY in many previous submissions; i.e., they have argued that the active moiety of a surfactant is the complex mixture of components, not a specific listing of "active" components. Due to the complex nature of the physical interaction of the components that results in the pharmacologic activity of naturally derived surfactants, the Division considers the entire mixture to be the active moiety. Further, the two surfactants are considered to be the "same" since they meet the criteria of being "closely related, complex, partly definable drugs with similar therapeutic intent" as stated in the Orphan Drug Regulations.

C. SP-B Activity In Infasurf

Dr. Holm presented the preliminary results of the sponsor's in-vitro protocol to define the role of SP-B in the activity of Infasurf and Survanta. These preliminary data were submitted to the Agency on May 28, 1997. These data, on the surface, provide support to ONY's argument that SP-B is critical to the full activity of Infasurf. The sponsor did not present the data from their preliminary work with Survanta. These data appeared to show that partially de-proteinated Survanta (20% residual total protein content) was less active for both surface and ex-vivo activity than Survanta. These results provide support for the activity of the protein fraction of Survanta; however, the study is not adequate to determine whether this activity is due to SP-B, SP-C, or both.

DIVISION AND OFFICE CONCLUSIONS AND RECOMMENDATIONS

For all the reasons outlined above and in the April 22, 1997, memorandum, the Division and Office continue to believe that Infasurf and Survanta are the "same" drug for Orphan Drug exclusivity purposes and that the sponsor has not demonstrated that Infasurf is clinically superior to Survanta, or that Infasurf makes a "major contribution to patient care" that is not provided by Survanta. We recommend that ONY's appeal of these determinations be rejected and that NDA 20-521 not receive final approval for marketing until July 1, 1998, when the period of Orphan Drug exclusivity granted to Survanta expires.

cc:
NDA 20-521
HFD-570/Division File
Jenkins
Bilstad
Himmel
Poochikian
Nashed
Kuzmik

APPEARS THIS WAY
ON ORIGINAL