SCIENTIFIC ROUNDS
Presented by the Division of Pulmonary and Allergy Drug Products
January 24, 2001

Title: Use of Placebo-Controls in Life Threatening Diseases:
Is the Developing World the Answer?

The efficacy and safety of a new drug that treats a serious and life threatening illness in premature infants will be studied versus sham/placebo in Latin America. The sponsor plans to apply for FDA approval, in addition to local and European registration. There are approved therapies (surfactants) for this illness (Respiratory Distress Syndrome, or RDS) in those countries where this trial is proposed to take place, and surfactants are even used in some of their hospitals. However, surfactants are completely unavailable to infants at many other hospitals, secondary to rationing or economic limitations.

Conduct of a placebo controlled surfactant trial for premature infants with RDS is considered unethical in the USA. The Division of Pulmonary and Allergy Drug Products has worked with the sponsor re: alternative trial designs. It appears that a non-inferiority approach may not be an option, add-on/withdrawal trial designs are not options, and a superiority trial design versus an approved therapy presents a clinical efficacy hurdle that the sponsor deems too high for this drug. The sponsor cites potential pharmacological advantages for this new synthetic surfactant over existing animal-derived and synthetic products, that may or may not translate into clinical benefits.

This Scientific Rounds will address ethical and regulatory questions and concerns that are generalizable to any drug used to treat a serious illness, in which it will be studied versus "standard of care" or placebo in an economically disadvantaged country.

Marianne Mann, M.D. Deputy Director, Division of Pulmonary and Allergy Drug Products, ODE II, will moderate this session. The format for this Scientific Rounds is:

Introduction	Robert Meyer, M/D. Division Director, DPADP
Approved Pulmonary Surfactants	Marianne Mann, M.D.
Case Presentation, Current Regulatory Guidance	Debra Birenbaum, M.D. Medical Officer, DPADP

Perspective of an Ethicist and
Lessons Learned from the African HIV Trials

Christine Grady, RN, PhD
Head, Section on Human
Subjects Research,
Dept of Clinical
Bioethics, NIH

Panel Questions/Discussion

Panel Members include:

Robert Temple, MD
Susan Ellenberg, PhD
William Rodriquez, MD
Martin Himmel, MD
Steven Hirshfeld, MD
Christine Grady, RN, PhD

Questions to Panel:

1. **Is it ethically acceptable to study Surfaxin versus placebo in premature infants with RDS in Latin America, where surfactant therapy is not universally available?**

2. **Are there changes in sponsor plans that would sufficiently ameliorate ethical concerns?**

3. **Who should determine whether or not a trial is ethical – officials where the trial is to be conducted and/or the international community?**

4. **What is our regulatory role in promoting the ethical conduct of trials performed abroad, in which the sponsor plans to seek USA approval?**

5. **If a placebo-control design is not acceptable, can we insist the sponsor find an alternate trial design which is ethical, or risk non-approval in the US?**

6. **What is our obligation to identify a path forward for this sponsor? Do we need more surfactants?**

A PLACEBO CONTROLLED SURFACTANT TRIAL FOR PREMATURE INFANTS WITH RESPIRATORY DISTRESS SYNDROME (RDS) IN LATIN AMERICA

Debra Birenbaum, Medical Officer, HFD 570
CDER Scientific Rounds
January 24, 2001

I. BACKGROUND

A. The sponsor proposed NON-INFERIORITY trial designs versus Survanta are found inadequate to support future NDA application.

- Efficacy endpoints in past trials were highly variable and inconsistent.
- Current treatment effect sizes are not reliably known.
- An acceptable delta, or preserved percentage of the effect size for a mortality endpoint in premature infants has not been determined.

B. A Surfactant superiority trial versus Exosurf in the USA and/or Europe is not considered feasible by the sponsor.

- Patient enrollment difficulties and "ethics" were cited as impediments to such a trial in developed countries.

- The sponsor has not yet provided justification for why they haven't planned a superiority trial versus Exosurf in **underdeveloped** Latin American countries.

C. Other Surfactant superiority protocol trial design alternatives are also not considered feasible by the Sponsor.

- Although the sponsor believes that Surfactant is superior to other drugs in its class in its non-clinical characteristics, the sponsor can't assume that it will be superior on clinically relevant endpoints (e.g. mortality, incidence of RDS). All surfactants contain DPPC, which the sponsor maintains is the primary source of surfactant efficacy.

- The Sponsor does not believe that Surfactant can demonstrate superiority in a prophylaxis versus rescue trial design alternative. Current practice will not allow for delays in treatment that might be necessary to demonstrate such superiority.

D. **The Sponsor has submitted a placebo-controlled Surfactant protocol in Latin American regions where other drugs in its class are approved, but not standard of care because of financial limitations or government rationing. Features of this protocol include the following:**

1. Multi-center, randomized, masked, two-arm study in 650 premature infants with RDS (325 patients per arm)

2. Patients will be randomized to receive either Surfactant or "sham air", with otherwise identical study procedures.

3. Primary endpoint is all cause mortality at 28 days at age

4. U.S. trained neonatologist teams will be sent to help ensure SOC comparability between Latin American and U.S. patients

5. A scientific advisory board, an independent DSMB with authority to halt the trial for safety and/or overwhelming efficacy, and a Steering Committee that will include Latin American individuals is planned.

6. The Sponsor will make Surfactant available at a reduced cost to the participating centers in Latin America following local approval.

E. A non-inferiority Surfactant RDS EUROPEAN trial versus Curosurf is also planned by sponsor.

- A complete protocol to be used in a European trial has not been submitted to the IND.

- The sponsor plans to seek drug approval in Latin America, Europe and the U.S., based on the results of these trials.

III. AREAS OF CONCERN

A. LATIN AMERICAN DATA APPLICABILITY TO THE USA POPULATION

- **Differences in standard of care relative to the U.S. and the effect of substandard care on mortality.**

1. The high 30-40% mortality rate in premature infants seen in these economically disadvantaged institutions may not reflect only surfactant-related SOC differences

2. An institution may not be able to correct other aspects of substandard care, even if they receive training by U.S. trained neonatologists.

3. Uncorrected maternal factors and prenatal management differences in care between Latin America and the U.S. may affect neonatal mortality.

B. ETHICAL ISSUES

1. Premature infants with RDS suffer a severe, life threatening illness for which they will not receive known, approved therapy that is SOC elsewhere in the world, and SOC even within other institutions in their own countries.

However in a placebo controlled Surfactant trial,

- Children receiving Surfactant treatment may receive benefits of therapy that outweigh the risks of trial enrollment – potential benefits this population in Latin America would not otherwise have received.

- Moreover, the Sponsor offers plans to make Surfactant economically accessible in participating countries following local approval and currently approved surfactants are not financially accessible to these patients.

- Neonatology training provided by the sponsor to local health care professionals may improve local standard of care for all babies.

2. Infasurf gained marketing approval by demonstrating superiority over Exosurf, when placebo controlled trials in the US were no longer possible. A superiority trial versus Exosurf would leave no infant untreated.

However,

- Superiority trials versus Exosurf may require larger patient enrollment and take longer to complete, thereby delaying potential for local approval and accessibility of effective therapy to underdeveloped areas in the host countries.

- Trial design would not address the relative effect of Surfactant, a synthetic prdouct, to animal-derived drugs in its class.