May 9, 2003

Bernard Schwetz, DVM, PhD
Acting Director
Office for Human Research Protections
1101 Wooten Parkway, Suite 200
Rockville, MD 20852

Re: HHS Review of Research under 45 CFR 46.407: "Characterization of Mucus and Mucins in Bronchoalveolar Lavage Fluid from Infants with Cystic Fibrosis"; University of North Carolina-Chapel Hill, Dr. Terry Noah, Project Principal Investigator

Dear Dr. Schwetz,

Please find below my opinion regarding the above referenced protocol after my review and discussions with other experts that occurred on May 5, 2003.

In Cystic Fibrosis (CF), a prevailing hypothesis is that the lungs are essentially normal at birth, but quickly within the first year of life become infected and have increased inflammation. This initiates the "vicious cycle" of CF lung disease, where infection and inflammation lead to lung tissue destruction, which further leads to difficulty clearing infection, and so on.

There is accumulating *in vitro* evidence that the ion transport defect associated with CF itself can predispose to the chronic lung infection, perhaps at the initiation of the vicious cycle. To ultimately help in the understanding and treatment of CF, these data require *in vivo* confirmation, with the expectation that such confirmation will guide development of future treatment strategies for CF lung disease. Given that CF lung disease is progressive, such intervention would be most powerful and potentially beneficial early in life.

There is currently no suitable animal model to study the initiation of CF lung disease. Thus, the only currently available "system" in which to study these events *in vivo* in a relevant and meaningful way is in infants with CF.

Given these considerations, the investigators propose a logical, thoughtful, appropriately designed protocol where infants with CF will undergo bronchoscopy with sedation around the time of neonatal diagnosis, and again at 6 months and 12 months of age to allow the investigators to obtain bronchoalveolar lavage (BAL) and mucus samples that will be assessed for biochemical, histologic, and microbiologic characteristics, with the expectation that these characteristics will allow better definition of the early events in CF lung disease. These data are critical in the understanding and potential amelioration of CF lung disease.

I fell that the study design minimizes risk to the subjects by having a sound research design that does not unnecessarily expose subjects to risk. Flexible bronchoscopy is a standard procedure in infants and children that is used for the diagnosis of infection and airway anomalies. Bronchoscopy is typically performed with sedation to minimize discomfort. In skilled hands, the major risk of the bronchoscopy is difficulty breathing with sedation, with lesser risks of minor nose bleeds, temporary hoarseness, and self limited fever after the procedure. The risk of sedation is minimized with appropriate monitoring of vital signs and oxygenation, provision of supplemental oxygen, and targeting the level of sedation to "conscious" or "moderate" where airway protective reflexes are maintained. I concur with the investigator's notion that three bronchoscopies are necessary to obtain the maximal amount of useful data. Limiting the protocol to 2 bronchoscopies at a 9 month interval would decrease the likelihood of being able to distinguish between, for example, a recent *versus* more remote acquisition of infection. The investigators have also expressed that they will coordinate obtaining BAL samples with a clinically indicated bronchoscopy where possible.

I feel that the selection of subjects is equitable, given that all subjects with CF identified in early infancy will be eligible. I also feel that the risks to the subjects are reasonable (as detailed below) with respect to the importance of knowledge that

may reasonably be expected to result from this research, with attention to additional safeguards suggested below aimed at further minimizing risk.

I do not feel that bronchoscopy with sedation can be considered minimal risk (46.404). The risk of difficulty breathing with sedation exceeds that which would be inherent in everyday life.

The investigators, and a subcommittee of the CF Foundation Data Safety Monitoring Board has argued that participation in this trial has the prospect of direct benefit for the subjects, and therefore would be approvable under 46.405. I agree with their contention that bacterial culture of BAL samples is the "gold standard" for assessing microbiologic colonization and infection of the CF lung, and that there is ample evidence that the more usual (and less invasive method) of deep throat culture has high false positive and false negative rates. There is also evolving sentiment in the field, based primarily on anecdotal data at this point, that early, aggressive antimicrobial therapy may be beneficial to subjects with CF by delaying the initiation of the "vicious cycle." However, there is also concern that such early, aggressive antimicrobial therapy may portend a later increase in antibiotic resistance. While I do agree that one bronchoscopy may afford the opportunity to identify an otherwise unsuspected pathogen in the lung of an infant with CF, I am less persuaded that participation in the trial would afford the possibility of direct benefit that is not available outside of the research, and therefore do not feel that this protocol is approvable under 46.405.

46.406 provides for approval of studies that are greater than minimal risk without the prospect of direct benefit if:

- the risk is a minor increase over minimal risk
- the knowledge obtained would aid in ameliorating a disorder or condition
- the experiences are reasonably commensurate with those of a child with the said disorder or condition
- the data are likely to yield generalizable knowledge

As discussed above, I feel that this study is likely to yield vital generalizable knowledge regarding CF lung disease that would potentially allow amelioration of this disorder in the future. Also, as part of the local practice at the CF Center at the University of North Carolina-Chapel Hill, apparently ~75% of infants less than 1 year of age will undergo bronchoscopy for clinical indications. While this is admittedly higher than many other CF centers, this practice reflects that Center's experience with bronchoscopy in infants and their use of early, aggressive, organism directed antimicrobial therapy in CF with cultures of BAL fluid serving as the best source of material. Thus, undergoing bronchoscopy for a child with CF who is less than 1 year of age as part of a study protocol is reasonably commensurate with the experience of a similar child with CF who is not a part of this study.

Thus, in my opinion, the approvability of this study under 46.406 hinges on whether bronchoscopy with sedation performed 3 times over the first year of life can be considered a minor increase over minimal risk. The position of the IRB at the University of North Carolina-Chapel Hill was that this procedure was more than a minor increase over minimal risk. The investigators have provided complication data for over 2000 bronchoscopies with sedation performed in children at their center since 1998, with 432 of these performed in children less than 12 months of age. Their complication rate was far less than 1%, with no reported serious complication. Even when only the children <12 months of age were considered, the complications rate remained less than 1%. With the presence of a dedicated, experienced bronchoscopy team, that the investigators who will be performing these procedures are very experienced, and their documented low complication rate with lack of serious complications, that this procedure, can, in my opinion, potentially be considered a minor increase in minimal risk. I therefore feel that, with attention to a number of additional safeguards delineated below, this study would be approvable under 46.406.

There are a number of issues that I feel should be clarified or addressed prior to final approval of the study:

- The protocol and consent form are incongruent with regards to the presence of an anesthesiologist. The consent form suggests that one will be present. Given the investigators' experience and low complication rate with procedural sedation, I do not feel that the presence of anesthesiologist is required. This should be clarified.

- The targeted level of sedation should be explicitly stated, and the procedure should be aborted if such a level cannot be achieved or is exceeded.

- Maximum amounts of sedative agents should be delineated, and the procedure aborted if inadequate sedation is achieved with this.

- A maximum amount of topical lidocaine (7 mg/kg) should be added to the protocol to decrease the risk of lidocaine toxicity.

- Intraprocedural stopping rules should be formulated with regard to:
    - Oxygen saturation. A suggestion would be saturation below 90% with supplemental oxygen.
    - Apnea
    - Bradycardia
    - Hypotension (with sedative agents)
    - Laryngospasm
    - Bleeding

  The consent form should delineate these stopping rules as well.

- Will a subject be removed from study if a bronchoscopy and BAL is not successful?

- The investigators should give a time window in which a clinically indicated bronchoscopy can substitute for a protocol bronchoscopy.

- The protocol states that samples will be stored for future study. The consent should have a separate check box for permission, as well as delineating a mechanism by which the samples can be removed from this repository, and a statement that future use of these samples will require a separate IRB review of the proposed use. It should also be stated whether a subject would remain eligible for study if storage of samples is refused.

- An independent safety monitoring committee comprised of experts in CF and bronchoscopy should periodically review safety data related to the bronchoscopy procedure. There should be stopping rules that would terminate the study if too many complications or adverse events were to occur. The CF Foundation DSMB is one example of such a committee.

- I feel that reimbursement for travel expense and compensation for time and inconvenience of $100/bronchoscopy is reasonable, however, I feel that receiving an extra $50 at the completion of the study may be a coercive inducement to undergo the last bronchoscopy. It also should be stated that the compensation will be provided even if the bronchoscopy is stopped for safety reasons

I also have a number of areas for clarification in the consent form.

- Page 2. While the purpose of the study is to try to evaluate the CF airway before children develop infection, in fact, some children may be infected before the first bronchoscopy. This should be reworded.
- Page 2. How will identity be protected on the videotape? There should be a separate check box to allow videotaping of the bronchoscopy.
- As discussed above, the discussion of sample storage should be expanded.
- Page 3. What will be done if the heart rate slows? As discussed above, criteria should be developed for termination of the procedure.
- Page 4. I feel that it is appropriate to say that the fever associated with bronchoscopy should disappear within 24 hours.
- Page 4. As discussed above, I do not feel that this study provides the possibility of direct benefit.
- Page 5. There is a typographical error for the on call Pulmonolgist's phone number (area code "191" instead of "919").

Respectfully submitted,

Ronald C. Rubenstein, MD, PhD
Assistant Professor of Pediatrics
University of Pennsylvania School of Medicine
Division of Pulmonary Medicine and
Vice Chair, Institutional Review Board
Children's Hospital of Philadelphia