

Shanghai Health Study

Issue: Consistent with standing Executive Committee guidance regarding proposed significant changes in the Shanghai Health Study (SHS), your concurrence is sought for the Benzene Health Research Consortium (BHRC) Oversight Committee's recommendations set forth herein.

Background: During its conference call of December 18, 2006, the API Executive Committee approved an increase in the funding for the Shanghai Health Study of \$9.1 million, to a total of \$35.2 million. This increase is contingent upon: the five participating companies committing to funding levels covering the increase; amending the study parameters to include an enhanced Quality Assurance program, and tying study payments to metrics of progress towards study completion.

Since the study's inception, the University of Colorado's Health Sciences Center has been the primary research organization, and has been funded via a grant. The University of Colorado has had a sub-agreement with Fudan University in Shanghai for the use of laboratory space and personnel. Due to a shift in the lab management within Fudan University, it is necessary to execute a new agreement for the continued operation of the lab. The participating companies have now learned that, at some point in early April, there will be a critical gap in the funding of the lab for expenses such as salaries. If this funding gap is not addressed, we are told the lab might be shut down and the completion of the study jeopardized.

Dr. Richard Irons, the University of Colorado's representative and a co-principal investigator of the study, has proposed that a significant portion of the remainder of the study be completed through Cinpathogen, Inc., a US for-profit corporation established for this purpose, of which Dr. Irons and another investigator are the two principal directors. Dr. Irons has indicated that Fudan University is in favor of this new arrangement, and that he has entered into formal agreements through Cinpathogen with Fudan University to coordinate and manage the laboratory to complete the Shanghai Health Study. API is awaiting documentation from Dr. Irons. Separately, Cinpathogen and the University of Colorado have stated in a joint letter that they will cooperate to manage the research going forward and finalize the study. This approach is designed to ensure the current operation of the laboratory and its continued existence after completion of the study (one of the tangential benefits that the participating companies are hoping to achieve). Publications from the supported research would reference all institutions involved in the study.

API has yet to receive a formal, final proposal from either Cinpathogen or the University of Colorado for the completion of the study. Nonetheless, the participating companies have recommended that API work as expeditiously as possible toward executing a contract with Cinpathogen and executing an amended grant with the University of Colorado to complete the Shanghai Health Study. This recommendation recognizes

that appropriate supporting agreements, including those between API and the five participating companies to increase the funding, would need to be executed as well.

Also, the participating companies have recommended that the API Executive Committee approve up to a \$2 million advance from API to Cinpathogen for the operation of the laboratory through June, 2007, prior to final contracts being executed. The Oversight Committee believes that this is a compelling, time sensitive situation due to the laboratory funding issues in Shanghai, and that immediate attention is required. Without this advance, Dr. Irons informed API that the lab will be closed or the study interrupted. Additional payments would be provided subsequently under contract to keep the study sufficiently funded, consistent with the approved budget and commitments from the participating companies.

Given time pressures in the study, concurrence of the API Executive Committee is sought at this time for proceeding down this new funding path, contracting with both the for-profit corporation, Cinpathogen, and the University of Colorado, rather than exclusively through the University. Contracting with Cinpathogen to complete the study may raise questions about the appropriateness of a for-profit entity replacing much of the University of Colorado effort in the conduct of such health research. Further, the addition of a newly formed, for-profit entity to the research effort would be administratively more complex than simply extending the existing contractual arrangement with the University of Colorado. However, Dr. Irons has informed us that this new administrative arrangement is supported by Fudan University and necessary under the current situation. While a new for-profit company will now become involved, there will be no change in personnel, and there are already for-profit entities involved in other parts of the study. Considering the options, the participating companies have recommended proceeding to engage Cinpathogen to help complete this study.

Action Requested

Your concurrence in the BHRC Oversight Committee's recommendations, as follows:

1. Approval for API to contract with the for-profit corporation, Cinpathogen, to complete a substantial portion of the remainder of this study. The Cinpathogen contract would be executed once fully developed proposals from the investigators and recommendations from the participating companies regarding those proposals are all received and once the participating companies have committed to funding the study.
2. Approval for API to advance up to \$2 million to Cinpathogen for the operation of the laboratory through June, 2007, prior to final contracts being executed, so long as this funding is consistent with the approved budget and commitments from the participating companies.

4/6/2007

Note from the GCSP Chair - Charlie Williams
Subject: Shanghai Health Study

The GCSP reviewed the current recommendations of the Shanghai Health Study Oversight Committee. Because of the time pressures only myself as Chairman represented the GCSP. The position paper furnished by API is quite accurate and factual. Further, on behalf of the GCSP, I am recommending and supporting the advance payment of \$2million dollars to ensure survival of the lab and staff to complete the study.

However, I think it is the responsibility of the GCSP to inform you on some additional risks/considerations. There is a wide variation of opinion amongst various staff and Companies involved in this study. The Over-Sight Committee has worked diligently and is aware of these risks/considerations. They include:

- 1- As indicated in your information note, the sudden involvement of Cinpathogen - a for-profit company that has Dr. Irons, a co-principal investigator, also as a principal in the company. Dr. Irons has indicated the Fudan University prefers working with CinPathogen rather than the University of Colorado. Dr. Irons has informed the Oversight Committee that a contract is in place between CinPathogen and Fudan, although neither API nor the committee has seen the contract. The University of Colorado and Dr. Irons have jointly signed a letter to API and the committee indicating that they will be providing separate, but complementary proposals to finish the study. Colorado will retain 2 subcontracts in support of the study. Initially Cinpathogen wanted the University of Colorado dropped entirely.
- 2- Dr. Irons has been unclear relative to his fixed cost needs and what deliverables are tied what costs. Many numbers provided simply do not add up. He has been particularly unclear in what is required to maintain the lab until new contracts are in place. The current payment is based on the best estimate of the Over-Sight Committee with what data they have available.
- 3- No new contracts have been available for API review and thus payment of this advance will only be covered by a short letter agreement yet to be resolved.
- 4- The Over-Sight Committee has developed a new QC and phased payment plan. This is a great step forward. However, this plan does not include pay-for-performance and payments that are tied to QC results. This may be able to be corrected in the final contracts. But even in the best case, the Over-Sight Committee is concerned about the level of their QC review and the plan will not guarantee delivery.
- 5- Thus far only half the cases as prescribed by the protocols have been delivered. The new promise is that all the cases should be delivered in the final remaining year. I think most feel that full delivery of cases is unlikely.
- 6- Ownership of the data is with the University of Colorado and most likely will be transferred to Fudan or CinPathogen and likely we have no ownership interest
- 7- The Over-Sight Committee has taken the position that this is the final year of case accrual, with data analysis in 2008 and publications then being produced regardless of the results delivered.

Certainly Dr. Irons is working under difficult circumstances and many trust in his promise to deliver. However, I think it is important for the EC to realize that it is very difficult to achieve normal commercial leverage in this situation. The current funding with Colorado is through a grant; the new funding is recommended to be through a contract with CinPathogen. There is a risk that we will end up at the end of this new contract period

having spent the full funds and with the project still not delivering the original promise. It is assumed that publications will be generated on what data is available.