

From: Methvin, Stacy P SCC-DCA
Sent: Sunday, December 17, 2006 8:38 PM
To: Hofmeister, John D SHLOIL-CA
Cc: Clegg, Patsy M SCC-DCS/22; Simpson, Edward J SCC-DCA/2
Subject: Shanghai Health Study - Dec 17 2006.ppt
John,

On Monday I will be calling you to discuss the attached slides on the Shanghai Health Study (benzene exposure analysis). I understand that you have a telecon with API later in the day where this subject will come up. There was an important meeting last week where the members of the consortium which provides funding for this project discussed the recent request for a 40% increase in funding. Shell's response is due on January 5. At this time I am inclined to approve given the conditions that have been set forth although I am surprised at the large increase in the fifth year of the study. I will be able to give you the key points of the situation and give you the opportunity to ask questions.

Stacy

Shanghai Health Study

Sponsor: Benzene Health Research
Consortium

Update December 2006

Shanghai Health Study

Program Overview

- 5 Sponsors (Shell, ChevronTexaco, ExxonMobil, ConocoPhillips, BP)
- Three studies shown on next slide
- Benzene and leukemia/lymphoma epidemiology
 - Benzene exposure estimation in Shanghai community.
 - Leukemia/lymphoma epidemiology - a science based approach to understanding disease progression of a complex family of diseases:
- Total contracted cost to date is \$27 MM
 - Shell's share to date is \$5MM.
- Oversight Committee met on Dec. 13-14 to review additional request for funding up to \$10.4 MM, \$2 MM Shell share
 - Recommendation to grant \$9.1 MM additional funds with conditions set for meeting program objectives, companies must respond by January 5. BP and Exxon have agreed their funding.

Study Scope: Health Effect Study of Benzene in Shanghai

**AML/NHL
Case Control
Study**

**AA/MDS/AML/B
P
Disease
Progress
Study**

**Molecular
Epidemiological
Study
of Benzene
Exposure**

**Joint Sino-US Clinical and Molecular Laboratory
(JCML)**

Shanghai Health Study – December 15, 2006

Study Areas	Desired Objectives	Current Status
○ Case control	500 cases of AML and NHL	425 AML / 240 NHL cases
○ Molecular Epi	Biomarkers for disease	Factory worker evaluations
○ Disease Progression	Knowledge in benzene poisoning and MDS progression to AML	40 % AMLs / NHLs followed

Options considered by Sponsors

No additional funding	Fully Fund Request	Reduce risk of study not getting completed within new funding request Recommended Option
Cost limited to current - \$5 MM (Shell share)	Shell share increased to \$2MM	Support additional funding if conditions met
Contractual exposure if Shell does not fund	Future \$ increases unknown due to lack of requirements	Shell Share increased by \$1.7MM
Reputation management	End of study not guaranteed	Defined end of study YE '08

Shanghai Health Study – December 15, 2006

- Conditions defined by consortium in order to support additional funding:
 - Robust QA/QC process to be implemented; led by Dr Rice, Scientific Review Panel chair, with Dr. Wong, Case Control Study principal investigator and Judy Baldwin, professional QA/QC expert. QA/QC Team has full access to study database.
 - Case Control study accruals to achieve 500 AMLs and 500 NHLs or end by YE07 – whichever comes first
 - Progress on Disease Progression and Molecular Epi studies based on funding
 - Grant payments to University of Colorado tied to study progress
 - University of Colorado funding capped
 - Benzene Health Research Consortium (BHRC) to terminate YE08
 - Monthly metrics on case accruals reported to Scientific Review Panel and BHRC Oversight Committee

Shanghai Health Study – December 15, 2006

- Remaining Study Time Line
 - 2007: Complete data collection
 - 2008: Data analysis
 - Closing Ceremony in Shanghai (cultural and ethics expectation)
 - Sponsors consortium terminates
 - 2008-09: Publications

Shanghai Health Study Sponsor Review

December 2006

December 2006 Review

- Drivers for sponsoring study
- Accomplishments
- Funding challenge
- Elements for consideration
 - Technical assessment
 - Contracts and commitments
 - EA
- Options
- Recommendation

Drivers for sponsoring study

- Case Control:
 - Better dose response for benzene exposure and link to AML and NHL
 - Good epi data for risk assessment/regulation
- Disease progression: relationship of non-cancer diseases of the bone marrow and AML
- Molecular epi: relationship of benzene exposure and potential early indicators of exposure and effect

Accomplishments

- State of the art molecular diagnostic laboratory servicing the Shanghai community
- 7 publications
- 1st study to use WHO tumor classification scheme
- AML and NHL subtypes identified
- Large AML and NHL cohort identified, but not yet reached protocol estimates of 500 each
- Tissue bank and supporting database for cases

Funding challenge

- To the best of our knowledge (as of Nov/Dec 2006):
 - Total budget request from \$ 26 Million to estimated \$ 34 - \$ 36 Million (~ added \$ 2 million from Shell)
 - Increase due to unexpected:
 - Staff retention difficulties.
 - Case shortfall due to hospital(s) out of protocol compliance with respect to patient information. Extend case accrual beyond Dec 06 to Dec 07 or longer. Costs largely due to diagnostic laboratory.
 - High end of budget range includes ~ \$ 1.2 million for transition from consortium funded laboratory to independence.

Elements for Consideration

- Technical assessment
 - Full study objective closure unlikely (regardless of funding), with possible further extension requests.
 - Uncertain incremental added value with added funds.
 - i.e., SMR (Standardized Mortality Ratio)
 - <1 – no link between exposure and effect
 - 1-2 - ?
 - >2 – link between exposure and effect
 - Higher than expected difficulties in exposure assessment in addition to infrastructure issues (i.e., case accrual protocol compliance).

Elements for Consideration

- Contracts
 - API/Shell contract
 - “Joining the Research Group commits each company to pay its full portion of the total costs of the completed program.”
 - API/University of Colorado Grant
 - “This is grant is being provided to accomplish the research as set forth in the most recent versions of the research protocols and criteria document.”
- EA

Options

1. Honor current commitment
2. Optimize cost options with alternative proposals such as stop case accrual mid 2007.
3. Support request for additional funding
 - Seek support from DS, RDS
4. Other?

Recommendation