

To: BHRC Technical Committee (E-mail) <benzconsort-tc@api.org>
From: Matt Todd <ToddM@api.org>
Cc: Matt Todd <ToddM@api.org>; Jim Vail (E-mail) <brec@rockbridge.net>; Bruce Jarrot <jarrotb@api.org>
Bcc:
Received Date: 2003-02-19 19:40:46 GMT
Subject: BHRC Technical Committee: Irons Progress report

BHRC Technical Committee Members:

Attached is Dr. Irons progress report and Workplace Inspection Form (mentioned in Jim Vail's email message below). These documents will be posted on the Technical Committee page on the Shanghai Health Study website. In addition, the Second Level Questionnaire Documents will also be made available on the website by the end of the week. Thanks.

Matt Todd
BHRC Communications

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-----Original Message-----

From: Jim Vail
Sent: Thursday, February 13, 2003 11:07 AM
To: Matt Todd
Subject: Irons Progress report

Matt: I am attaching the original version of the Irons progress report and in this case, I would like you to put it in the Technical Committee website and email them that it is available. Also, please let them know that we will try to obtain the missing "workplace inspection form" and will post this to the website, once in hand.

Thanks for your help,

- Jim -
> [Matt Todd]

Attachments:

Bilingual Worksite Inspection 1.doc
DB EA EP Prog Rep2.doc

PROGRESS REPORT
JANUARY 2003

**I. ANALYSIS OF DISEASE PROGRESSION FOR APLASTIC ANEMIA,
MYELO-DYSPLASTIC SYNDROME, ACUTE MYELOGENOUS LEUKEMIA
AND BENZENE POISONING IN SHANGHAI, CHINA**

**II. MOLECULAR EPIDEMIOLOGY OF BENZENE-EXPOSED WORKERS IN
SHANGHAI, CHINA**

A MULTICENTER INTERNATIONAL STUDY

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Dept. of Pharmaceutical Sciences, School of Pharmacy
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University of Colorado Health Sciences Center, Denver, CO.

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School of Public Health, Hua Shan Hospital, Cancer Hospital,
Fudan University Medical Center, Shanghai, China

I. INTRODUCTION

A. Executive Summary

1. Overall Status of Budget

NOTE: All of the budget projections cited in this report are derived from the updated budget projections provided to API in September 2002. A copy is included in appendix A for your convenience.

The overall status of the budget for this fiscal year is as follows: As of December 31, 2002 we have received \$7,515,759 against a current budget of \$4,617,530, exclusive of field expenses. Of the \$4,617,530, \$3,248,834 has been paid as of December 31, 2002 with \$888,121 sequestered for payment. This leaves a balance of \$480,575.

Table 1. Budget Summary

Category	Budgeted ¹	Spent	Unpaid	Difference
Personnel	\$745,300	\$710,788	\$0	\$34,512
Operating Expenses	\$391,593	\$305,422	\$4,396	\$81,775
Subcontracts	\$1,918,659	\$1,025,372	\$663,525	\$229,762
Travel	\$23,947	\$8,647	\$0	\$15,300
Equipment	\$1,210,213	\$899,642	\$219,057	\$91,514
Indirect	\$327,818	\$298,963	\$1,143	\$27,712
TOTALS	\$4,617,530	\$3,248,834	\$888,121	\$480,575

¹The budgeted amounts are the sum of each category from Dec-01 through Dec-02.

The unpaid operating, equipment and overhead expenses are transactions in progress as of 12/31/02 that require the funds to be encumbered. The unpaid subcontracts include \$372,225 due to EMBSI for year 2, and \$155,660 and \$99,989 owed to EMBSI for the SRP approved increases in their budget for years 1 and 2, respectively. Approximately, \$35,651 is required to complete the Children's Hospital's contract through 12/31/02 for a total of \$663,525 in unpaid budgeted contract funds. The \$255,649 due EMBSI as a result of the post SRP budget can only be paid upon revision of the API contract with UCHSC to include post- SRP related costs.

We have maintained a positive budget balance through successful negotiations with equipment and supply vendors. In addition, in order to minimize shipping costs, we have contracted with Asian distributors when possible. Travel expenses incurred by the trainees were reduced by minimizing the number of trips that the trainees took between UCHSC and JCML.

2. Projected

We currently see no need to modify the projections for Jun-03 as stated last year (appendix A). There will be increased supply costs to stock the laboratory with clinical supplies/reagents, however, the budget carryover into the Jan-Jun -03 budget period will be sufficient to pay for these costs.

3. Budgetary and contractual issues

To date, API has not provided UCHSC with contract addenda to reflect the modified budget changes following the SRP review. Therefore, we cannot modify our contracts and payment schedule to EMBSI to reflect their actual costs schedule.

II. EQUIPMENT

A. Overview

All equipment that is necessary for the startup of JCML laboratory operations has been received. The TQ-Prep System is in process for shipment and is expected to arrive at JCML by March 1, 2003. Additional equipment and/or subcontracts are currently being evaluated as a means to enable JCML to better support Chinese occupational benzene worker examinations. The resolution of these issues will be addressed in the next progress report. Installation of flow cytometry, hematology Cell-Dyn and immunoanalysis equipment, as well as microscopes, has been completed. Final installation of cytogenetics equipment has been delayed due to reagent import issues but is expected to be completed before the end of February.

B. Budget

Table 2. Equipment Summary

Vendor	Equipment	Budgeted	Paid	Unpaid	Status
Abbott	Blood analyzer	\$65,000	\$65,518		At JMCL
Abbott	IMx (HIV/HBV/HCV)	\$20,000	\$20,000		At JMCL
Beckman Coulter	Centrifuges	\$34,750	\$45,035		At JMCL
Beckman Coulter	Flow Cytometer	\$162,500	\$145,965		At JMCL
Beckman Coulter	TQ-Prep (sample prep for Flo			\$34,660	In Process
China So Technology LTD	Ventana Discovery/Benchmark /Special stains units	\$205,000	\$220,000		At JMCL
Gene Company	Imaging system	\$195,000	\$195,000		At JMCL
Gene Company	Thermal Cycler	\$10,000		\$6,500	At JMCL
Gene Company	Denaturation /Hybridizat System for FISH	\$5,000	\$10,500		At JMCL
Great Systems Tech	Deionizer Water System	\$5,000	\$16,268		At JMCL
Rae Systems	Benzene Monitors	\$20,000	\$20,000		At JMCL

Scientific Instrum Co	Olympus Microscopes		\$28,145		At UCHSC
Taiyo Koeki	Olympus Microscopes	\$65,000	\$48,195		At JMCL
Tecan US	Coverslip harvester	\$29,500	\$30,500		At JMCL
Tech-Knowledge Solutions	Slide stainer/Lyophlizer/Refrigerator	\$25,554	\$33,510		At JMCL
Thermatron	CDS-5 Drying Chamber	\$12,000	\$16,950		At JMCL
Thermo Life	Incubators/laminar hoods/freezers/rate freezer/liquid storage/alarm system	\$195,957		\$172,573	At JMCL
S&F (Shanghai) International Trade Co., Ltd.	Electrophoresis /Transfer set	\$ 5,000		\$4,134	At JMCL
Total		\$ 1,055,261	\$895,586	\$217,867	

C. Supplier Agreements

JCML has completed agreements with Gene Company (Vysis), Genetime Technology, Inc., American International Medicine, Inc., and Tech-Knowledge Solutions. Reagents such as FISH probes, monoclonal antibodies, cell culture reagents as well as general laboratory supplies are easily obtained. In addition, agreements for clinical supplies are in process and will be completed by March.

Gene Company distributes products in China for the following companies:

AB Gene	Integra Biosciences
Affymetrix	Kimberly-Clark
AMS: Mmunokontakt	Kontes& Kimbles
Becton Dickenson / Falcon	Miltenyi Biotec
BioWhittaker BioTrin	Molecular Probes
BioWest	Oncogene Research
Calbiochem	Partec
CLP	Pierce
Continental Lab Products	Qiagen
Corgenix (Reaads)	Robbins Scientific
DAKO	Santa Cruz Biotechnology, Inc
Eppendorf	Schleicher& Schuell
Epicentre Technologies	Treff
Genset	USA Scientific
Hyclone	Vysis
Intergen, Inc.	Worthington

Genetime Technology, Inc. distributes products in China for the following companies:

ABgene	JT Baker
Amresco	Labnet
Arista Biologicals	Neuro Probe
Biodesign	Omega Biologicals
BiosPacific	Origene Technologies
Cell Signaling Technology (CST)	PBL laboratories
Chemicon	Peptotech
Clontech	porex
Corning	Pragmatics
Endogen	R&D
Fitzgerald Industries	RDI (Rapid Diagnostics/ICN Biomedical)
Hyclone	Rockland
Immunetics	Sigma
Intergen/Serologicals	Trevigen

III. LABORATORY

A. Personnel

The startup phase of laboratory personnel training at UCHSC is reaching completion with the last two trainees scheduled to return to Shanghai in late March/early April. Recruitment of personnel necessary for laboratory start up is virtually complete. Methods standardization and validation of laboratory procedures is underway at the present time.

B. Database

Server computer hardware has been installed at Fudan University and UCHSC. Serial application for moving data from the Cell-Dyn to the Server has been developed and will be deployed on the PC networked with the Flow Cytometer and Cell-Dyn. Configuration and testing of the Server & Serial port application is underway. Core clinical applications are almost completed including laboratory management, patient accession and testing with clinical forms and exposure assessment components in final stage of development. Questionnaire and exposure assessment modules are also nearing completion. We have adopted a Bar code system to facilitate sample identification and patient accession.

IV. SUBCONTRACT SUMMARY

Table 3. Subcontract Summary

Subcontracts	Budgeted	Spent	Unpaid	Difference
1 Fudan	\$538,525	\$404,538	\$0	\$133,987
2 SIPHS	\$139,995	\$124,059	\$0	\$15,936
3 SMCDP	\$154,716	\$80,175	\$0	\$74,541
5 EMBSI	\$982,374	\$354,000	\$627,874	\$500
6 Children's Hospital	\$103,049	\$62,600	\$35,651	\$4,798
TOTALS	\$1,918,659	\$1,025,372	\$663,525	\$229,762

Due to a central government-mandated reorganization, certain functions previously provided by IPHS are being reassigned to SMDCDP and Fudan University. Accordingly, we will be redistributing resources necessary to support these activities over the course of the next quarter. We anticipate that, with minor exceptions, this will be a “budget-neutral” exercise.

V. BENZENE METABOLITE PILOT STUDY

We have conducted the planned pilot study to develop and evaluate a sensitive method for the analysis of benzene metabolites in human blood and bone marrow. After initial developmental work, we ultimately have settled on a liquid-liquid extraction method coupled with electron capture GCMS. Using this method we have successfully quantitated phenol, catechol and hydroquinone in blood and bone marrow of human subjects not occupationally exposed to benzene. We have standardized and validated the procedure with cold labeled isotopes and established standard curves for each analyte in small volumes of blood and bone marrow. Precision, accuracy and sample stability have also been determined. This study was an unqualified success and has resulted in the development of a very sensitive and reliable method that is currently being transferred from UCHSC to the Shanghai CDC. A manuscript detailing the method is in the final stages of preparation and will be submitted to the SRP for review sometime in the near future. A second manuscript describing background levels and tissue distribution of benzene metabolites in unexposed subjects is also being prepared. We believe that these papers will provide new and fundamentally important information on the metabolism of benzene and its metabolites in humans that will have an immediate and significant impact on the field. Methods of analysis for PMA and tt-MA are being developed at this time.

VI. EXPOSURE ASSESSMENT

Initial training for exposure assessment was begun in September, based on English materials translated to Chinese and presented in Mandarin at Fudan University. The course covered an overview of the projects, and details on exposure assessment for subject work histories and related workplaces. The primary course goal was to prepare the inspection teams to develop information

about the exposure history of subjects from the case-control and DP studies (CC-DP). This exercise resulted in a re-evaluation of our strategy to integrate procedures that incorporate existing Chinese approaches and has led to a much more collaborative process among the participating organizations. Hands-on training for rudimentary ventilation system checks was conducted using smoke tubes and UltraRAE selective detectors. These instruments were delivered to IPHS in September.

Following the course, we redesigned the workplace inspection form that guides the collection of fundamental information needed to support retrospective assessment of exposures. This form is now bilingual, and has been tested by actual workplace interviews of workers. (Copy of form attached). We plan on providing and retaining this form electronically via the study database. We will use it for wider orientation and on-site training of additional IPHS staff in January and February.

Personal exposure monitoring is not yet a national standard in China. That will have to be adopted by CDC and Fudan as part of our project requirements. We will provide training on designing and conducting personal monitoring-based exposure surveys. Recruitment and training of Exposure Assessment Team personnel is underway at Fudan University and should be complete by the end of February/early March.

The primary questionnaire for use in the CC-DP studies is in the database in bilingual form. Data entry into a test version of the database has been completed, with no significant changes needed. Minor changes are being evaluated to facilitate language issues.

We are designing an extracted version of the questionnaire that will be obtained from the database for use in assessing exposure history. We plan to have that summary of work history and exposure –related information from the questionnaires flow electronically to the exposure assessment committee. The extract will give the exposure assessment teams the information relevant to the subject’s workplace, possible materials to which they were exposed, and information on their tasks. The summary will not include confidential information, such as medical history.

Several additional initiatives are underway, via graduate student research projects or via contacts elsewhere in China. These include analysis of consumer paint exposure surveys and the application of expert elicitation and uncertainty analysis using Bayesian statistical approaches for dealing with subjective data in an exposure assessment.

VII. EPIDEMIOLOGY

We have refined and clarified epidemiologic design and site selection strategies for the Molecular Epidemiology study. We have conducted several pilot tests of Disease Progression interview procedures in order to improve questionnaire design and have performed second level pilot testing to evaluate and train in-hospital questionnaire takers. In addition, we have initiated training of clinical coordinators and established instructions for the selection and recruitment of subjects and controls. Final training of clinical coordinators will be conducted at the end of February/beginning of March.

We have initiated and guided a study to characterize previous acute benzene exposures in Shanghai that will aid in the conduct of ME Phase 1 and the selection of factories in Phase 2a. In

addition we have established a Factory Selection Committee and provided procedures for selecting factories to include in the ME study. This has included drafting ME abstraction forms for Phase 1, and questionnaires for Phase 2. The latter has now been fully integrated into the clinical examination form used by CDC in conducting benzene worker physical exams.

VIII. REGULATORY HARMONIZATION AND LICENSING

Final COMIRB and Fudan IRB approval was obtained for protocols and informed consent forms as of November 2002. However, last minute modifications in IC for the Molecular Epidemiology study and new consortium requirements for incremental ERP and SAP review necessitate one more round of approvals. We hope to be able to submit these changes to COMIRB as soon as possible in order to have the opportunity to start the studies in March. If we are unable to begin recruitment of cases in March, scheduling difficulties may require that we postpone startup to April or even June. During the fourth quarter of 2002 I also traveled to Beijing to meet with Chinese central government officials and the Ministry of Health. They provided me with important information that we previously did not have on licensing requirements for foreign research collaborations and laboratories. Fudan University and JCML have applied for and are in the process of obtaining the necessary licenses for operation.

Appendix A.

Budget Projections provided to API in September 2002

	Dec-01	Jun-02	Dec-02	Jun-03	Dec-03	Jun-04	Dec-04	Jun-05	Dec-05	Jun-06	Dec-06	Totals
Personnel												
Budgeted	\$172,140	\$224,883	\$348,277	\$331,316	\$293,007	\$282,480	\$297,450	\$293,713	\$310,768	\$298,684	\$244,179	\$3,096,897
Operating Expenses												
Budgeted	\$13,131	\$94,401	\$284,061	\$198,373	\$259,003	\$228,529	\$268,289	\$252,851	\$301,653	\$277,143	\$151,160	\$2,328,595
Subcontracts												
Budgeted	\$123,629	\$688,452	\$1,106,578	\$549,014	\$988,733	\$449,506	\$934,456	\$453,377	\$860,043	\$415,102	\$202,694	\$6,771,584
Travel												
Budgeted	\$0	\$8,429	\$15,518	\$11,340	\$4,127	\$3,418	\$4,245	\$0	\$1,852	\$1,945	\$0	\$50,873
Equipment												
Budgeted	\$291,568	\$253,578	\$665,067	\$0	\$350,000	\$0	\$0	\$0	\$0	\$0	\$0	\$1,560,213
Indirect												
Budgeted	\$47,922	\$111,454	\$168,442	\$140,668	\$144,596	\$133,751	\$148,196	\$142,107	\$159,711	\$150,221	\$102,788	\$1,449,855
TOTALS												
Budgeted	\$648,390	\$1,381,197	\$2,587,943	\$1,230,711	\$2,039,465	\$1,097,683	\$1,652,637	\$1,142,048	\$1,634,027	\$1,143,094	\$700,822	\$15,258,017