

**From:** Bruce Jarnot <jarnotb@api.org>  
**Sent:** Tuesday, March 8, 2005 7:06 PM (GMT)  
**To:** benzconsort-tc@listserve.api.org  
**Cc:** benzconsort-oc@listserve.api.org  
**Subject:** BHRC-TC... Pls Reply: Conf Call to review DP/ME Progress Rpt, 4Q04 Expense Rpt  
**Attach:** DPME\_ProgRpt\_budget\_03-07-2005.pdf

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**Benzene Health Research Consortium (BHRC) Technical Committee (TC) -**

Attached is a pdf copy of Dr. Irons' year-end 2004 (YE04) Shanghai Health Study DP/ME Progress Report, which arrived last night (pages 7 & 8 were intentionally blank).

**Please reply with your availability & time preference to join a 1-hour TC conference call this Friday, March 11th**, to  
1) review the three YE04 progress reports (Fudan & CC Reports are available on the SHS web site) and 2) review the draft 4Q04 Financial Report. Friday's call will provide Jennifer with a TC report for Monday's OC conference call (March 14th, 1:00pm EST):

**Yes \_\_\_ No \_\_\_** Fri Mar 11 at **11:00am** EST (10am Central, 8am Pacific)

**Yes \_\_\_ No \_\_\_** Fri Mar 11 at **1:00pm** EST (12pm Central, 10am Pacific)

**Yes \_\_\_ No \_\_\_** Fri Mar 11 at **3:00pm** EST (2pm Central, 12pm Pacific)

Ann Loudon provided a copy of UCHSC's 2004 Report of Expenditures today; I will distribute the draft 4Q04 Financial Report in a separate email, as soon as UCHSC's information is transcribed into this draft report.

Best Regards - Bruce.

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Bruce M. Jarnot, Ph.D., DABT  
American Petroleum Institute  
Regulatory and Scientific Affairs  
1220 L Street, NW (Suite 900)  
Washington, DC 20005-4070  
phone: (202) 682-8473 fax: -8031  
email: [jarnotb@api.org](mailto:jarnotb@api.org)

## **PROGRESS REPORT**

**January, 2005**

- 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
- III. EXPOSURE ASSESSMENT

### **A MULTICENTER INTERNATIONAL STUDY**

Molecular Toxicology and Environmental Health Sciences Program  
Dept. of Pharmaceutical Sciences, School of Pharmacy  
Department of Pathology, School of Medicine  
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

## Introduction

### I EXECUTIVE SUMMARY

#### A. Overall Status of Budget

Attached is an official summary of the overall budget for the year ending December 31, 2004.

During this past year we have witnessed a 150%-200% increase in case contact above our initial projections. This poses an enormous challenge for clinical and research laboratory operations. The resulting impact on case accrual is discussed in JCML Operations below. These have resulted in changes for JCML staffing and operations, resulting in an 188% increase in cash flow for this 6 month period compared to Jul03-Dec03 (\$880,342 versus \$468,341). To date, the increased cash flow has been largely masked in the overall budget, due to timing and commensurate adjustments. The overall status of the budget for the second half of this calendar year is as follows: We spent \$1,535,622 compared to a projected budget of \$1,652,636, resulting in net savings of \$117,014 in funds expended during this period (Table 1). This savings is largely due to economies we instituted at UCHSC by elimination of positions and reductions in operating expenses. These economies will result in continued delays related to report generation, analysis of data and publication schedules.

**Table 1. Budget Summary (Reporting Period)**

|                    | Budgeted <sup>1</sup> | Expenditures | Variance   |
|--------------------|-----------------------|--------------|------------|
| Personnel          | \$297,450             | \$229,260    | \$68,190   |
| Operating Expenses | \$268,289             | \$237,258    | \$31,031   |
| Subcontracts       | \$934,456             | \$948,696    | (\$14,240) |
| Travel             | \$4,245               | \$0          | \$4,245    |
| Equipment          | \$0                   | \$0          | \$0        |
| Indirect           | \$148,196             | \$120,408    | \$27,788   |
| TOTALS             | \$1,652,636           | \$1,535,622  | \$117,014  |

<sup>1</sup>The budgeted amounts are the sum of each category from Jul-04 through Dec-04.

**Table 2. Budget Summary (Entire Project)**

|                    | Budgeted <sup>2</sup> | Expenditures | Variance    |
|--------------------|-----------------------|--------------|-------------|
| Personnel          | \$1,949,553           | \$1,688,995  | \$249,558   |
| Operating Expenses | \$1,345,787           | \$1,225,006  | \$120,781   |
| Subcontracts       | \$4,840,368           | \$4,514,305  | \$326,063   |
| Travel             | \$47,076              | \$8,993      | \$38,083    |
| Equipment          | \$1,560,213           | \$1,383,490  | \$176,723   |
| Indirect           | \$895,028             | \$792,429    | \$102,599   |
| TOTALS             | \$10,638,025          | \$9,624,218  | \$1,013,807 |

<sup>2</sup>The budgeted amounts are the sum of each category from Dec-01 through Dec-05.

| Subcontracts                   | Expenditures (Dec 01 – Dec 04) |
|--------------------------------|--------------------------------|
| Fudan University               | \$2,654,541                    |
| IPHS                           | \$167,577                      |
| SMCDC                          | \$153,004                      |
| EMBSI                          | \$1,325,692                    |
| Children's Hospital Cincinnati | \$213,492                      |

## B. Budget Analysis

Our projected costs for the remainder of the project are outlined in Table 3. These projections are based on actual final year-end numbers rather than estimates and therefore are more accurate. These primarily reflect the increased JCML caseload together with some reallocation of resources necessary to replace industrial hygiene capability originally subcontracted elsewhere and to conduct exposure assessment. Based on our current rate of cash flow, we will exhaust our current balance together with currently scheduled April and October, 2005 payments by June, 2005. Therefore, immediate changes in payment scheduling are necessary in order to forestall a default that will result in cessation of JCML operations. UCHSC operates on a budget-based system, which means we can expense funds in accordance with our previously agreed upon budget just so long as encumbrances are not exceeded. Once totals exceed the agreed upon schedule we no longer pay bills. Fudan operates on a cash and carry system, with all expensed funds matched by money in the bank. Salaries are eliminated first, then supplies, then operating expenses.

**Table 3. Projected Budget (Remainder of Project)**

|                    | Year 2005   | Year 2006   | Year 2007 ** |
|--------------------|-------------|-------------|--------------|
| Personnel          | \$463,610   | \$482,155   | \$203,265    |
| Operating Expenses | \$501,380   | \$396,360   | \$0          |
| Subcontracts*      | \$2,286,533 | \$1,958,069 | \$150,000    |
| Travel             | \$1,000     | \$1,000     | \$0          |
| Equipment          | \$0         | \$0         | \$0          |
| Indirect           | \$251,158   | \$228,674   | \$52,849     |
| TOTALS             | \$3,503,681 | \$3,066,258 | \$406,114    |

\*EMBSI Estimated additional costs are not included.

\*\*Post-study costs

According to UCHSC grants and contract procedures, we will need a letter **prior to April 30, 2005** outlining a new payment schedule and, a new total budget, if possible. Once again, please note that this is a budget-based project. Therefore, independent of a change in the total budget or commitment of funds an amendment letter is necessary to change budget schedule or allocations. Such a letter will also be sufficient to meet our deadline of April 30<sup>th</sup>.

At the request of API staff, we are providing, in order of preference, three different scenarios for re-structuring the payment schedule and to meet our deadline. All of the options replace the existing payment schedule after the 1 April, 2005 scheduled payment of \$874,030 which remains the same in all scenarios. Our preferred option is outlined in Table 4 and provides for additional scheduled payments in July, 2005 and February of 2006 and 2007, respectively.

**Table 4. Proposed Payment Schedule (Scenario I)**

| Proposed Payment Schedule |           |                             |
|---------------------------|-----------|-----------------------------|
| 1-Apr-05 \$               | 874,030   | Scheduled Payment           |
| 1-Jul-05 \$               | 2,500,000 | Scheduled Payment           |
| 1-Feb-06 \$               | 2,682,280 | Scheduled Payment           |
| 1-Feb-07 \$               | 406,114   | Scheduled Payment           |
| \$                        | 6,462,424 | Remaining Scheduled Payment |

Scenario II is outlined in Table 5, and provides for semiannual payments over the same time period.

**Table 5. Payment Schedule (Scenario II)**

| Proposed Payment Schedule |           |                             |
|---------------------------|-----------|-----------------------------|
| 1-Apr-05 \$               | 874,030   | Scheduled Payment           |
| 1-Oct-05 \$               | 2,500,000 | Scheduled Payment           |
| 1-Apr-06 \$               | 1,750,000 | Scheduled Payment           |
| 1-Oct-06 \$               | 932,280   | Scheduled Payment           |
| 1-Feb-07 \$               | 406,114   | Scheduled Payment           |
| \$                        | 6,462,424 | Remaining Scheduled Payment |

Because of the immediate time constraints, we are also providing a schedule to accomodate a temporary stopgap measure to alter the payment schedule within the context of the existing contract. This does not change the total budget commitment, but alters the agreed payment schedule and allows us to forestall the re-budgeting issue beyond April 30<sup>th</sup>, 2005. In order to do this we still need a letter amending the payment schedules prior to this date. We would then have to negotiate a new contract for the remainder of the project before April, 2006.

**Table 6. Payment Schedule (Scenario III)**

| Proposed Payment Schedule |           |                             |
|---------------------------|-----------|-----------------------------|
| 1-Apr-05 \$               | 874,030   | Scheduled Payment           |
| 1-Oct-05 \$               | 2,500,000 | Scheduled Payment           |
| 1-Apr-06 \$               | 996,120   | Scheduled Payment           |
| \$                        | 4,370,150 | Remaining Scheduled Payment |

## **II JCML OPERATIONS/STUDY PROGRESS**

### **A. Overview**

During our first full year of operation we diagnosed a total of 725 cases of hematopoietic and lymphoid diseases. At the time of this writing 687 have been independently confirmed and entered into the database, including 437 myeloid neoplasms, 155 lymphoid neoplasms, 55 AA and 50 nutritional anemias. This represents a 50% increase from our initial projected case contact rate. About an additional 50 cases remain to be confirmed from this first year series. Analysis of first quarter operations for the second year indicates an even greater case-contact rate of 250, bringing total case-contact to well over 1000 between Jun 03 and Dec 04. Consequently, for the second year of operation we are currently projecting diagnoses of between 750-1000 cases. As previously discussed, this increased rate of case contact has greatly increased cash flow requirements for JCML relative to initial projections. On the other hand, if case accrual continues at the same rate, the goals originally projected for study case accrual should be met for all diseases by the end of 2006.

### **B. Disease Progression**

a. As part of the DP study we have described a novel disease developing in a case series of individuals who were previously exposed to high concentrations of benzene (BZ). Patients were recruited based on a medical history of previous BZ hematotoxicity with several having been identified in ME Phase 2a. Subjects employed in the rubber, petrochemical, pharmaceutical, manufacturing or painting industries were referred to JCML with a previous history of BZ poisoning, and exposure to BZ was confirmed by: review of factory industrial hygiene monitoring records, real-time quantitative industrial hygiene analysis, including personal samples (N=325) and breathing zone analyses (N=225), and/or previous evidence of hydrocarbon intoxication and anecdotal descriptions of solvent use and composition. Subjects for which quantitative data was available were estimated to have full shift exposures averaging between 50 ppm and 300 ppm benzene for varying periods of time ranging from 6 to 22 years. Several features of hematopoietic disease in these individuals have not previously been described in cases of benzene toxicity and provide promising avenues for hypothesis-based studies on the pathogenesis benzene-induced hematotoxicity.

b. As part of the DP study, we also examined the prevalence of MDS subtypes in 100 consecutive cases presenting at Shanghai hospitals. The results were published in an abstract in Blood (104:4715. 2004). This study revealed significant regional variations, including a young median age (57 yr), and a relatively high prevalence of refractory cytopenia with multilineage dysplasia (RCMD) (53%) in Shanghai. The overall incidence of clonal cytogenetic abnormalities was 25%. The most frequently encountered lesions were trisomy 8, 20q-, 5q- and 7q-. These results provide a basis for comparison with BP cases. A manuscript describing these results is in preparation.

c. A comparable AML subtype analysis is underway, reviewing and correlating morphology, phenotype, cytogenetics and molecular characteristics of AML subtypes in Shanghai. Two manuscripts describing this work are in preparation at the present time: one deals with the overall frequency and prevalence of WHO AML subtypes in Shanghai, and the other characterizes the

prevalence of myeloid/NK cell subtypes which we evaluating in order to determine their significance with respect to our studies. We have also published an abstract on a case series of aggressive natural killer cell leukemia (ANKL), which is a rare neoplasm of NK cells associated with bone marrow failure and a dismal prognosis. Diagnosis was made using morphologic, immunophenotypic, cytogenetic, fluorescence in situ hybridization (FISH) and molecular data. The differential diagnosis of ANKL is complicated by the lack of clonal markers and morphologic and immunophenotypic heterogeneity, and this disease is often confused for AML.

### **C. Exposure Assessment**

In his progress report dated January 31, Professor Fu Hua provides a detailed outline and discussion of issues related to exposure assessment, which will not be repeated here. Exposure assessment remains our biggest challenge for a number of reasons, and adjustments are currently being implemented. These include: a) recruitment of additional personnel with advanced qualifications. At the present time two new individuals have been recruited including a student and a chemical engineer; b) increased participation of Western study personnel in management and conduct of exposure assessment activities, c) facilitation and encouragement of IPHS involvement by providing a more responsive and knowledgeable interface between Fudan and IPHS personnel. This should include a validation and critical review of IPHS database gaps that, ideally, should be suitable for publication; d) Improving guidance and oversight of QA/QC and questionnaire administration procedures, e) shifting emphasis from reliance on historical database and surrogate factory analyses to emphasize timeline, job-exposure matrix evaluations, and f) implementing more real-time model validation. This approach is described in detail in the original study protocol but has not yet been fully implemented.

### **D. Molecular Epidemiology**

Phase I summaries are being prepared from a group of 84 factories that have been selected with historical workplace monitoring data and 1800 workers for whom medical surveillance records are available. At present, a total of 48 factories have been found to match with IPHS records, and 400 medical records have been abstracted. Phase IIa analyses have been performed on 231 workers with relatively high workplace exposures. Recruitment of workers for Phase IIb analyses has proven difficult with only 3 individuals to date formally recruited via this mechanisms. Therefore, we integrated metabolite analyses into Phase IIa, and continue to implement a strategy designed into the original protocol that enables us to recruit BP cases from candidates originally identified in Phase IIa. Through this mechanism we have successfully recruited approximately 20 BP cases into the DP study, simultaneously providing detailed exposure evaluations of these individuals as well as clinical assessment. A manuscript describing our analytical methodology is in preparation.



