HealthTech IV

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Semiannual Report
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Submitted to:
United States Agency for International Development (USAID)

Submitted by:
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Table of Contents

Executive Summary

During the past six months, the HealthTech management team has interacted with USAID staff on multiple topics and issues. The most significant activity of the past six months is the extension of the HealthTech program for another five years with an additional authorization of $18 million to bring the total ceiling to $34,996,645. The scope of work for the next five-year period is a continuation of the successful approaches and strategies for research, development, and introduction of technologies for health, nutrition, and reproductive health.

At the same time, requests for funding from FY 2006 funds for new and continuing activities during FY 2007 have been submitted to the different strategic objective groups at USAID. At this time, the level of the cumulative budgets is unclear; USAID management is working with HealthTech to ensure at least the minimal level of funding to keep the program intact.

HealthTech has been called on frequently to provide technical expertise on topics related to other health technologies. During the past six months, we have interacted with USAID and other organizations on the following topics:

- HealthTech participated in a meeting called "Opportunities for Coordinated Research on Infection Prevention and Use of Chlorhexidine," with the Chlorhexidine Working Group. Michael Free presented a framework on translating research into products for global health. HealthTech is prepared to advise the group on commercialization of the product for use in developing-country markets. This may result in a more active project for HealthTech in the coming months.
- HealthTech has also provided USAID with some information relative to the production and use of zinc as a therapy for diarrhea. The advice related to addressing supply side and market development challenges.
- Informal meetings have been held between HealthTech staff and staff of the USAID-funded Hygiene Improvement Project (HIP) on topics of mutual interest related to water, hygiene, and sanitation technologies. One outcome of the discussions is a potential joint project between HealthTech and the University of North Carolina to validate and advance an HS2 test that a researcher there has developed. The overall goal of the project will be to optimize low-cost methods for determining the bacteriological quality of drinking water. Specifically, valuating the H2S method could yield either positive or negative results in regards to its ability to predict fecal contamination.
- PATH has received an allocation of funds from the Office of Population and Reproductive Health to produce a summary of the meeting held last fall called the Global Consultation on the Female Condom. Over 100 experts from 15 countries gathered to discuss the current status and recommendations concerning the female condom. This article will provide recent information about the female condom presented at the Global Consultation, including evidence on its effectiveness for prevention of sexually transmitted infections and pregnancy, issues related to expanding access and use, and gaps in the knowledge base. The article will be published soon as an issue of PATH's publication called *Outlook*.

The rest of this report includes highlights and milestones of various core projects during the past six months, followed by individual reports on each project. Not included are reports on other PATH projects that are funded basically as pass throughs. The staff of those projects (which currently include the Global Campaign for Microbicides and the Interagency Working Group on Gender Violence) report directly to their counterparts at USAID.

Highlights and Milestones of HealthTech Projects During the Past Six Months

- The Pfizer team, the suppliers of the main injectable contraceptive (depot medroxyprogesterone acetate [DMPA]) used by USAID in their family planning programs worldwide, has received senior management approval to move forward through production scale-up and registration of DMPA in the Uniject™* device. Pfizer is close to reaching agreement with BD, suppliers of the Uniject device. This result has been many years in the making.
- The cost-effectiveness evaluation comparing the use of different vasectomy methods in different countries was completed and a draft circulated to USAID, EngenderHealth, and Family Health International. It was determined that methods such as fascial interposition and thermal cautery, while requiring an additional investment in both training and materials, can provide increased cost-effectiveness as well as reduce the social impact of high rates of vasectomy failure.
- Formal stability studies of oxytocin filled into the Uniject device began in March 2006. Unless there are unexpected results, BIOL, the private-sector collaborator in Argentina, should be able to provide initial supplies of oxytocin in the Uniject device for field study use by late 2006/early 2007.
- Advancement of new cold chain technologies is progressing, with WHO PQS (Performance, Quality and Safety) specifications under final review, the SolarChill refrigerator ready for WHO approval, and the Twinbird refrigerator passing laboratory testing at PATH.
- The successful outcome of the screening and compatibility study of gentamicin in the Uniject device at BIOL, coupled with the subsequent initiation of the formal stability study, has marked a major milestone in the progress of gentamicin in the Uniject device development. The outlook for technical feasibility is excellent, although a definitive conclusion necessarily awaits data from the formal stability study.
- RBP-EIA test kits are now commercially available from the private-sector collaborator Scimedx. So far, 180 test kits have been sold to UNICEF and to Macro International for use in the demographic health surveys.
- Data collection in the Bolivia study of the rapid chlamydia test (CT) was initiated in January 2006. To date, nearly 1,800 women have been enrolled in the study.
- Preliminary experimental work with the fluorescence system has repeatedly shown a 10-fold increase in sensitivity of the CT test without a decrease in specificity. New prototypes are currently being developed in the PATH laboratory.
- HealthTech contributed to global waste management policy development in sessions at the 2005 SIGN meeting, the 2005 GAVI partners meeting, at meetings at WHO, and through teleconferences. Primary topics included policy guidelines, needle-remover approval, financing systems for medical waste, and equipment options.
- We completed development of a prototype low-cost needle remover that fits on found containers. This reusable device could reduce the cost of needle removers to around $5 by utilizing locally available containers, such as jerry cans or water jugs, as the needle collection container.
- An article entitled on a past HealthTech technology, “A Low-Cost, Color-Coded, Hand-Held, Spring Scale Accurately Categorizes Birthweight in Low-Resource Settings” has been published in the *Archives of Disease in Childhood*, a BMJ journal. The study is a joint study of Birthweigh III, originally developed under HealthTech, by researchers from PATH, the Johns Hopkins University, Saving Newborn Lives, and the Nepal Nutrition Intervention Project. The conclusions of the study

* Uniject is a trademark of BD.

were that this "low-cost, simple-to-use device classified infants into three weight categories with a high degree of consistency and accuracy that exceeds that of surrogate measures."

- TEMPTIME reports that in 2005 another 280,000,000 vaccine vial monitors (VVMs) were sold to vaccine manufacturers, half of which were used for oral polio vaccine and the other half for multiple other vaccines. UNICEF and WHO now estimates that use of VVMs on the basic vaccines alone could save about $5 million per year.

Strategic Objective 1

Introduction of Injectable Contraceptives in the Uniject Device

Goals of project

The goal of the project is to increase the safety, acceptance, and reach of depot medroxyprogesterone acetate (DMPA) injectable contraceptives in the Uniject™[†] device (hereafter called "DMPA-Uniject") for family planning programs. Such products facilitate innovative new options, such as home injection of contraceptives and applications related to outreach.

Status of project as of March 2006

The Pfizer team, the suppliers of the main product used by USAID in their family planning programs worldwide, has received senior management approval to move forward through production scale-up and registration. Pfizer and BD, the makers of the Uniject pouches, are hammering out final details of a long-term commercial supply and exclusivity agreement.

Achievements and progress in the past six months

Pfizer senior management has given approval for project go-ahead, which will entail an investment of approximately $40 million. Pfizer has completed technical and manufacturing feasibility investigation of full-scale production of their subcutaneous formulation of DMPA-Uniject with positive results.

Problems encountered and actions taken to resolve them

The BD-Pfizer negotiations for long-term supply and exclusivity agreement of the Uniject device for injectable contraceptives were not completed during this six-month period. The companies are working through the complex issue of the agreement and both are committed to moving the project forward; however, technical progress will not move forward until these issues are resolved.

Next steps and milestones expected in the next six months

- BD and Pfizer will hopefully conclude commercial negotiations.
- PATH will provide formal concurrence with the exclusivity terms of the BD-Pfizer agreement.
- After the BD-Pfizer agreement is signed, we will hold a collaborators' meeting including USAID, PATH, Pfizer, and BD to discuss collaborative activities in the next phase of work and plan a possible public announcement.
- PATH/HealthTech will provide USAID with an updated background paper on volumes and trends in supply of injectable contraceptives to international donor agencies for distribution in developing countries.

[†] Uniject is a trademark of BD.

Vasectomy Technologies

Goals of project

Under this project, PATH aims to:

- Verify that a cautery device (designated by the manufacturer as single use) is safe and effective for multiple uses.
- Provide technical assistance to other project partners for review of new devices, sourcing of generic devices, and sperm analysis.
- Conduct a cost-effectiveness evaluation for different vasectomy methods currently used.

Status of project as of March 2006

After completion of the cost-effectiveness evaluation and distribution of the written results to stakeholders, the project has reduced its level of activity to match its remaining funding.

Achievements and progress in the past six months

The cost-effectiveness evaluation, comparing the use of different vasectomy methods in different countries, was completed and a draft circulated to USAID, EngenderHealth, and Family Health International. It was determined that methods such as fascial interposition and thermal cautery, while requiring an additional investment in both training and materials, can provide increased cost-effectiveness as well as reduce the social impact of high rates of vasectomy failure. PATH/HealthTech concluded that, when possible, fascial interposition and thermal cautery should be introduced into existing vasectomy programs and trainings in order to maximize the cost-effectiveness of ongoing programs. New trainings should incorporate these methods in order to establish the most cost-effective country vasectomy program.

Problems encountered and actions taken to resolve them

No significant problems were encountered in drafting the report of this evaluation.

Next steps and milestones expected in the next six months

- PATH will draft a manuscript based on the cost-effectiveness evaluation and submit it to an open-source, peer-reviewed journal.
- Per discussions with PATH/HealthTech will conduct a basic bench assessment to evaluate the performance and reusability of a Canadian-made cautery device.

Strategic Objective 2

Oxytocin in the Uniject Device

Goals of project

Under this project, HealthTech aims to improve and ease adoption of active management of the third stage of labor (AMTSL) and therefore reduce postpartum hemorrhage (PPH) by engaging one or more pharmaceutical producers to develop and supply oxytocin in the Uniject™[‡] device (hereafter called "oxytocin-Uniject).

Status of project as of March 2006

Formal stability studies of oxytocin-Uniject began in March 2006. Unless there are unexpected results, BIOL, the private sector collaborator in Argentina, should be able to provide initial supplies of oxytocin-Uniject for field study use by late 2006/early 2007.

Achievements and progress in the past six months

- The screening and compatibility study of oxytocin-Uniject at BIOL was completed in December 2005. Results were acceptable, although some fluctuation in pH was observed which then lead to a minor refinement to the oxytocin formulation for the stability study.
- The formal stability study was initiated in March 2006. PATH/HealthTech and BIOL collaborated to specify production and QA/QC processes.
- HealthTech and the Prevention of Postpartum Hemorrhage Initiative (POPPHI), two PATH-managed programs, organized a seminal meeting that engaged drug standards/regulatory staff from US Pharmacopeia (USP) and WHO with experts in field use of oxytocin. HealthTech contributed substantively to the technical discussions leading up to and during the meeting, drawing in part on experience and data supplied by BIOL. As a result of the process, the USP specification of oxytocin for injection will likely be modified in two key respects: (1) to allow for product storage conditions as supported by the manufacturer's data, instead of specifying a single (and overly restrictive) storage condition for all; and (2) to allow for presentation in approved, alternative presentations other than ampoule (e.g., Uniject), according to USP senior staff.

Problems encountered and actions taken to resolve them

- The formal stability study was postponed approximately two months due to an unanticipated delay by BD (due to an internal miscommunication) in supplying the Uniject devices.
- Work on a broad landscape assessment of suppliers of oxytocin for injection (as a finished dosage product) was delayed. PATH had accepted an offer of help from WHO staff, but then the WHO staff were subsequently unavailable to collaborate.

Next steps and milestones expected in the next six months

- Three- and six-month data from the formal stability study will be available.
- Pending positive stability study results, HealthTech will work with BIOL to plan clinical trial lot production to meet the needs of any field studies requiring product in late 2006/2007 onward.
- PATH will assist BIOL in preparing a brief on manufacturing supply and cost of production scenario for oxytocin-Uniject, while continuing to liaise with potential field partners.
- BIOL will initiate drafting of regulatory documentation for their application to the Argentine FDA for registration of oxytocin-Uniject.
- The positive changes to USP standards for oxytocin for injection (described above) will be made. According to standard USP process, the changes will carry "draft" status until 2007.

[‡] Uniject is a trademark of BD.

Strategic Objective 3

Reducing Freezing of Vaccines in the Cold Chain

Goals of project

The goals of this project are to:

- Increase awareness of the extent and consequences of inadvertent vaccine freezing.
- Build global policy supporting freeze prevention.
- Facilitate development of new freeze-proof cold chain equipment.

Status of project as of March 2006

Evidence building and policy change activities continue. PATH visited Mozambique to initiate retraining on the cold chain in one province and held meetings with the national Expanded Programme on Immunization (EPI) to discuss priorities for freeze-prevention activities. Advancement of new technologies is progressing, with WHO Performance, Quality, and Safety (PQS) specifications under final review; the SolarChill refrigerator ready for WHO approval; and the Twinbird refrigerator passing laboratory testing at PATH.

Achievements and progress in the past six months

- PATH conducted cold chain training in Mozambique and held policy discussions on freeze prevention with national EPI.
- The Indonesian EPI presented out-of-cold chain and freeze-prevention policy at WHO Regional Office for South East Asia (SEARO) meeting. This policy was greeted with enthusiasm by member countries.
- HealthTech staff presented experience with cold chain and freeze prevention at the WHO Regional Office for Europe (EURO) meeting on the hepatitis B birth dose. Several countries expressed interest in adopting similar measures.
- HealthTech staff also presented similar material at the WHO seminar in Geneva and generated interest in developing both into WHO policies.
- PATH participated in the WHO PQS working group to develop specifications for a new refrigerator to prevent freezing.
- Laboratory testing of the Twinbird vaccine refrigerator was completed. The device meets WHO requirements and is ready for PATH field testing and WHO testing.
- Redesign of the SolarChill solar refrigerator was also completed. The device appears to meet WHO specifications and is ready for testing by WHO.
- HealthTech completed a market study of vaccine refrigerators and distributed the results to refrigerator manufacturers and United Nations partners.

Problems encountered and actions taken to resolve them

Delay in WHO finalization of PQS specifications for refrigerators is holding up finalization and market introduction of the Twinbird and SolarChill refrigerators.

Next steps and milestones expected in the next six months

- HealthTech will further disseminate the results of recent activities that have built evidence of freezing of vaccines in the cold chain. We will pursue national, regional, and global opportunities to publicize this information and create awareness of concerns about freezing of vaccines. Specific findings that will be ready for publication and dissemination in 2006 include:
  - Indonesia's success in eliminating vaccine freezing, including interventions and results.
  - Vietnam's study results and subsequent steps to eliminate vaccine freezing, including interventions and results.

  - Mozambique's study results and subsequent steps to eliminate vaccine freezing.
  - Bolivia's study results and subsequent steps to eliminate vaccine freezing.
  - Global review of published and unpublished literature demonstrating the breadth of reports of freezing in the cold chain.
- PATH/HealthTech is organizing a workshop on prevention of freezing of vaccines for six to eight Latin American country EPI and cold chain managers in collaboration with UNICEF Americas to be held in Panama City June 2006.
- HealthTech will assist in retraining health workers and implementing freeze-prevention strategies in the Mozambique study province.
- Staff will work with WHO to finalize and release policy guidelines to reduce freezing in the cold chain and to finalize and release policy guidelines regarding use of hepatitis B vaccine out of the cold chain.
- Results of the PATH China study showing effectiveness of strategy for taking hepatitis B vaccine out of the cold chain, conducted under other funding, will be published. PATH will assist with the Chinese policy shift to approve use of hepatitis B vaccine out of the cold chain with the Uniject™[§] device and vaccine vial monitors (VVMs).
- We plan to conduct a cost-benefit analysis of new refrigerators, looking at advantages offered through improved temperature control, reduced maintenance, and reduced fuel costs. The outcome will be used to support the case for programs to invest in new refrigeration equipment.
- A field evaluation of three Twinbird refrigerators in Indonesia will be conducted.
- We will assist the manufacturer in submitting the Twinbird refrigerator for WHO approval and will identify opportunities for larger-scale introduction of the Twinbird refrigerator into WHO, UNICEF, and Japan International Cooperation Agency (JICA) programs.
- PATH will identify funding and model program opportunities for introduction of the SolarChill refrigerator into public health program.
- We will also explore opportunities for an outreach vial cooler that could be used to cool reconstituted vials at outreach sessions. This would support WHO's policy of eliminating the need for ice throughout the entire cold chain.
- At the same time, we will continue to identify and evaluate other promising freeze indicator and cold box technologies.

[§] Uniject is a trademark of BD.

Sharps Disposal Technologies

Goals of project

The project goal is to advance, test, and introduce safe needle removal and sharps disposal systems for health centers and outreach services, in order to reduce the potential transmission of disease through the use of contaminated needles.

Status of project as of March 2006

Global prioritization of medical waste management is building as evidenced by a December 2005 GAVI meeting where HealthTech described its waste management activities. GAVI, WHO, and donors are seeking ways to address medical waste issues effectively. HealthTech has continued to engage in global dialogue on medical waste and is actively involved in planning global strategies.

Achievements and progress in the past six months

- HealthTech actively participated in a medical waste planning meeting among ministry of health and ministry of environment staff from 14 African and Caribbean countries, under the PEPFAR-funded MMIS project. The meeting defined acceptable practices, identified appropriate equipment, studies specific infrastructure needs, and provided policy planning guidance.
- HealthTech developed a training manual on sharps waste management. The manual features separate sections for health workers and for waste handlers. It contains trainers' notes, PowerPoint presentations, and graphic handouts. The manual has been distributed to all PEPFAR countries, WHO, and other partners in the medical waste field.
- HealthTech completed its mission as a member of the Performance, Quality, and Safety (PQS) working group on medical waste equipment. PATH's primary role was in developing specifications for needle removers.
- HealthTech contributed to global waste management policy dialogue in sessions at the 2005 SIGN meeting, the 2005 GAVI partners meeting, at meetings at WHO, and through teleconferences. Primary topics included policy guidelines, needle remover approval, financing systems for medical waste, and equipment options.
- We completed development of a prototype, low-cost needle remover that fits on found containers. This reusable device could reduce the cost of needle removers to around $5 by utilizing locally available containers, such as jerry cans or water jugs, as the needle collection container.
- HealthTech disseminated information on TechNet on the evaluation of needle collection barrels in Senegal and the study of a needle remover in a family planning program in Uganda.
- We hosted industry-UNICEF discussions and agreed to test syringe melters in 2005. The meeting led to an agreement for a manufacturer to develop a prototype, low-cost syringe melter that PATH would evaluate and field test.
- The paper on the 2003 India needle remover study called "Evaluating use and acceptability of needle-remover devices in India" has been accepted for publication by *Tropical Doctor* and will be published soon.

Problems encountered and actions taken to resolve them

WHO review of existing needle-remover data concluded that insufficient evidence is available on device safety to make policy recommendations. HealthTech will continue to work with WHO to collect additional field data to guide policy decisions.

Next steps and milestones expected in the next six months

- Develop policies and guidelines and adopt effective sharps management technologies and practices.
  - With WHO, we will continue to advance global consensus on medical waste management best practices. HealthTech will provide technical guidance in the development of equipment selection guides and national planning processes.

  - We will engage international agencies such as GAVI and the World Bank to develop strategies and funding mechanisms for sustainable implementation of medical waste systems.
  - HealthTech will continue to assist WHO on a GAVI-funded series of meetings in Africa to develop national health care waste plans for GAVI countries.
  - We will develop technical guidance materials for needle removers and disseminate them via PEPFAR countries, and TechNet.
  - We will continue the field evaluation in Senegal of low-cost needle removers using found containers. The results of the study will indicate acceptability of the devices and the need for further design refinements.
  - HealthTech, with cofunding from other sources, will conduct an analysis of successful needle-removal and recycling system used in Andhra Pradesh State, India, and disseminate the results.
  - HealthTech staff will use the Safe Injection Global Network (SIGN) and TechNet meetings to disseminate updated information and encourage feedback on improved practices in sharps management strategies and technologies.
- As needed, we will develop refinements to needle removal, such as alternatives for sharps disposal, that will reduce costs. Health Tech will work with developers of needle-remover devices to refine their own designs.
- HealthTech will plan and conduct a value analysis and opportunity review for syringe melters. This will involve identifying developers of syringe melters, establishing agreements to test their devices, conducting field evaluation of devices in Indonesia, and then disseminating the findings.
- Over the next six months, we will identify successful uses of nonburning disposal systems, such as autoclaving or shredding. We will document introduction issues and disseminate lessons.

Gentamicin in the Uniject Device

Goals of project

The goal of this project is to create a sustainable supply of gentamicin in the Uniject™[**] device (hereafter called "gentamicin-Uniject") so this innovative combination can be fully evaluated for use in the treatment of neonatal infections.

Status of project as of March 2006

The successful outcome of the screening and compatibility study of gentamicin-Uniject at BIOL, the private-sector collaborator in Argentina, coupled with the subsequent initiation of the formal stability study, has marked a major milestone in the progress of gentamicin-Uniject development. The outlook for technical feasibility is excellent, although a definitive conclusion necessarily awaits data from the formal stability study.

Achievements and progress in the past six months

- The screening and compatibility study at BIOL was completed in December 2005.
- Frontage Laboratories' analysis of gentamicin active pharmaceutical ingredient (API) from four different sources was completed in November. All four API manufacturers' drug master files for gentamicin API are current with the USFDA.
- Results from the screening and compatibility study and the analysis of gentamicin API from different sources resulted in identification of two promising buffer systems, two promising API sources, and one alternate API source.
- The protocol and preparations for the formal stability study were completed, stability lot production undertaken, and the formal study initiated in March. PATH and BIOL collaboratively planned and reviewed the batch production, QC, and QA processes.

Problems encountered and actions taken to resolve them

- The stability study start-up was postponed two months due to a delay by BD in shipping the Uniject devices to Argentina. As a result, filling of the Uniject devices by the contractor MR Pharma had to be rescheduled from December 2005 to February 2006.
- BD, BIOL, and PATH have identified the source of confusion on the shipping documentation that lead to the delay.

Next steps and milestones expected in the next six months

- Three- and six-month time-point data from the formal stability study will be available. These time points will include data from gentamicin-Uniject stored under accelerated conditions.
- Pending positive stability study results, we will start planning production of a clinical trial lot of gentamicin-Uniject to meet the needs of any field studies requiring product in late 2006/2007 onward.
- PATH will assist BIOL in preparing a brief on manufacturing supply and cost of production scenario for gentamicin-Uniject.
- BIOL will initiate drafting of regulatory documentation for their application to the Argentine FDA for registration of gentamicin-Uniject.
- PATH will work with Saving Newborn Lives to clarify the timeframe and product needs of potential field studies in Bangladesh and/or additional countries.

[**] Uniject is a trademark of BD.

Neonatal Resuscitation

Goals of project

The goal of this project is to increase understanding and awareness of the availability and performance of neonatal resuscitators among the international community and to enhance availability of appropriate devices in low-resource settings, particularly in Africa and Asia.

Status of project as of March 2006

During the past six months a thorough search of global inventories of neonatal resuscitator devices has been conducted; the results provide a solid foundation for further activities related to increasing the availability of appropriate devices in Africa. A collaborative activity to assess newborn resuscitation skills, equipment, and logistics and supply systems has been initiated.

Achievements and progress in the past six months

- A manuscript on bench/user evaluation of eleven devices has been completed and submitted to a peer-reviewed journal (*Archives of Childhood Disease*).
- Abstracts submitted to the Global Health Council on the context of use survey and bench/user evaluation of devices were not accepted; abstracts were resubmitted to the upcoming American Public Health Association annual conference.
- Provision of technical assistance to resuscitator manufacturers in Africa and Asia has been initiated and has resulted in: (1) a subcontract with F2N, the Indonesian company that manufactures tube and mask devices, which will be developing an affordable device for the Indonesian market; (2) initiation of discussions with Adcock Ingram, the South African manufacturer of the Samsons Disposable Neonatal Resuscitator, regarding the possibility of expanding their portfolio of devices.
- A global inventory of available neonatal resuscitation devices has been completed; a compendium of details of over 100 identified devices is forthcoming.

Problems encountered and actions taken to resolve them

- At the request of the Government of India (GoI), the proposed evaluation of a national neonatal resuscitator training program has been shifted to a situation analysis of essential newborn care, although the primary component remains neonatal resuscitation. This increased scope will require additional funding which GoI indicates it has available for this task. However, it is not clear how quickly these funds can be accessed.
- At the request of USAID, the planning for the joint WHO technical meeting on neonatal resuscitators was halted.

Next steps and milestones expected in the next six months

- A manuscript on the context-of-use survey will be submitted to a peer-reviewed journal.
- Procurement and limited bench testing of over 100 devices identified in the global inventory will be carried out in order to determine the most appropriate devices for low-resource settings.
- Initiation of discussions with manufacturers of the most appropriate devices identified through the global inventory process will be started in order to determine a suitable commercialization strategy for the African region.
- A market assessment of existing and/or redesigned devices in select African countries will be conducted.
- The collaborative effort with the GoI, USAID/India, the National Neonatology Forum, WHO, and PATH India to conduct a situation analysis of essential newborn care (primarily neonatal resuscitation) in selected districts in India will be planned and launched.

Retinol Binding Protein Enzyme Immunoassay (RBP-EIA)

Goals of project

The goal is to enhance the reliability and ease of vitamin A deficiency (VAD) assessment and decrease the associated cost. Specific objectives are to improve the consistency of results of vitamin A assessment, including ease of specimen analysis and interpretation, and to improve the reliability of VAD estimates.

Status of project as of March 2006

We have officially started the phase of introduction of the RBP-EIA into the public health arena this year. Scimedx has shipped test kits directly to users for survey work and to researchers for their evaluation, who will provide us with feedback on the ease of use. We are currently supporting new users in the field, such as the Demographic Health Surveys (DHS) in Uganda. We are also seeking ways to engage USAID and partners to raise awareness of the test for use in upcoming surveillance activities to assess VAD.

Achievements and progress in the past six months

- RBP-EIA test kits are now commercially available, and 180 test kits have been sold to UNICEF and to Macro International for use in the demographic health surveys.
- Worked successfully with Macro International to use RBP-EIA in 2006 DHS survey in Uganda.
- Final reports on the technical evaluations of the device in Guinea-Bissau, Senegal, Tanzania, and Zimbabwe have been received and reviewed.

Problems encountered and actions taken to resolve them

- UNICEF in Myanmar requested test kits; however, some of the samples had been compromised. A.J. Cope, the supply agent for UNICEF, had already submitted a purchase order to Scimedx, and, therefore, the tests were shipped. The tests will not be used in Myanmar until they can verify that some of the samples are still robust, or they will decide to use them on new samples.
- Potential users have noted an insufficient volume of conjugate in the test kit and have made the suggestion to provide the three calibrators in three different tubes and to dilute them in the same way as the serum samples are diluted. We are currently in discussion with Scimedx to identify the options for increasing the conjugate volume and for providing three separate calibrators.
- There continues to be interest in using the RBP-EIA with dried blood spots (DBS). Macro International is currently using the RBP-EIA in their DHS survey using DBS, and we hope that this will provide us with new information to inform this application of the test. In addition a researcher from the University of Washington is currently conducting experiments on the effect of the elution factor for DBS results using the RBP-EIA. They have also completed a paper summarizing the effects of storage temperature/time on the stability of RBP in DBS.

Next Steps and milestones expected in the next six months

- We will meet with staff from the USAID nutrition office and USAID-supported programs, such as A2Z, to identify possible uses of the RBP-EIA in upcoming vitamin A surveillance work.
- We will address issues raised by end users and work with Scimedx to make the test kit easier to use by increasing the conjugate volume and putting the calibrator into three separate tubes.
- HealthTech will continue to obtain end-user feedback and incorporate feedback into making the test kit easier to use.
- We will interact with Scimedx to introduce them to potential users and jointly support promotional opportunities.
- We will facilitate easier sample collection and use in the field by providing technical support, finalize job aids, and provide support to new users.
- Validation results will be published and shared with the scientific community and other interested groups.

Strategic Objective 4

Immunochromatographic Strip Test for Chlamydia

Goals of project

The goals of this project are to:

- Establish commercial availability of a rapid chlamydia (CT) test for use in developing countries.
- Publish data supporting the utility of this test in the developing world.
- Achieve endorsement of the test by the World Health Organization.

Status of project as of March 2006

The CT Immunochromatographic Strip (ICS) test prototype has been developed and optimized and was sent to Bolivia for a large field evaluation, which is ongoing. We are also in contact with individuals at Emory University and the Global Network for Perinatal and Reproductive Health about conducting introduction and evaluation studies in South Africa and Colombia respectively. Additionally, we have started preliminary work on a new fluorescence-based signal enhancement system, which may provide greater sensitivity for the CT test.

Achievements and progress in the past six months

- Data collection in the Bolivia study was initiated in January 2006. To date, nearly 1,800 women have been enrolled in the study.
- Preliminary experimental work with the fluorescence system has repeatedly shown a ten-fold increase in sensitivity without a decrease in specificity. New prototypes are currently being developed in the PATH laboratory.

Problems encountered and actions taken to resolve them

- In the Bolivia field trial, there were difficulties with laboratory quality assurance on the reference assays at one of the field evaluation sites. To remedy this problem, we worked with our Bolivian collaborators to improve the consistency and standards of the laboratory work at the clinic. Recent data from the clinics is much improved.

Next steps and milestones expected in the next six months

- The Bolivia field study will be completed and the data analyzed.
- We will begin writing manuscripts from this data for publication in peer-reviewed journals.
- A policy recommendations report will be generated for presentation to the Bolivia Ministry of Health.
- We will continue development of our prototype fluorescence-based rapid diagnostic test.

CD4+ Cell Count Diagnostic Project

Goals of project

Our goal is to develop a simple, semiquantitative test for monitoring CD4+ cell counts in HIV-positive populations. This technology will:

- Allow health care workers to quickly and accurately monitor the immunological status of their HIV-positive patients.
- Provide data for clinicians making important decisions about initiating, stopping (through structured treatment interruption), or changing antiretroviral therapy drug regimens.
- Eliminate the most important barrier to appropriate distribution of drug therapies that reduce morbidity; reduce viral load, and therefore reduce transmission; and most importantly, empower clinicians and patients to control the expanding epidemic.

Status of project as of March 2006

By September 2005, with cofunding from the Doris Duke Foundation, we had developed a colorimetric membrane and simple modified glucometer detection system for ascertainment of CD4+ cell counts. However, this system proved inadequate at the lower end of the cell count range, so we are continuing the research and development to find solutions, now partially supported with USAID funds under HealthTech.

Achievements and progress in the past six months

- The detection system has been reoptimized to include the use of fluorescent particles, which provides a greater dynamic resolution of signal in this system.
- Evaluation of five membrane types for use in the system has been completed. We evaluated several different membrane types with differing levels of porosity and internal structure for use with the system. We have selected a single membrane for use with the system.
- Evaluation of alternative purification systems that involve both magnetic particles and fluorescent beads prior to detection has been completed. We have successfully eliminated the need for temperature controlled incubation during sample processing steps.
- PATH has procured a flow cytometer for use as a gold standard during iterative product development. It will be used to validate the precision of our prototype assays.

Problems encountered and actions taken to resolve them

- We initially had difficulty quantitatively determining the difference in signal intensity of fluorescent spots on our prototype membranes. In collaboration with the PATH product development shop, we developed a digital camera and computer-based system for getting real time estimates of assay sensitivity and consistency.
- We did not fully understand the fluid and binding characteristics of the assay steps. We evaluated these with a fluorescent microscope purchased for a separate project in the lab. This allowed us to troubleshoot some unexpected problems in the assay.

Next steps and milestones expected in the next six months

- Over the next few months, we will procure a set of HIV-positive blood specimens from either the University of Washington or the University of California, San Francisco, for use in testing the device in the PATH labs. This will require protocol development and approval from PATH's Human Subjects Protection Committee.
- We expect to complete further optimization of the purification and detection systems.

Microbicide Applicator Project

Goals of project

The goal of this project is to ensure that safe, appropriate, affordable applicators are available for use in low-resource settings at the time of microbicide introduction.

Status of project as of March 2006

In December 2005, HealthTech received a written response from the USFDA in regards to the pre-investigational new drug (IND) submission that we made in September 2005. This submission included a protocol for a "bridging study" for evaluating the equivalence between a user-filled paper applicator and a prefilled plastic applicator, as well as specific questions regarding the validity of this data for a sponsor's new drug application to the FDA. Based on this response from the FDA, we are now proceeding with the two initial bridging studies set forth in the protocol.

Achievements and progress in the past six months

- A collaboration agreement with Profamilia, our Dominican Republic clinical study partner, has been negotiated, and the clinical study protocol and data collection forms completed. This study will assess user compliance, acceptability, dose delivery, and safety of user-filled paper applicator with KY Jelly.
- A protocol for a comparative dose delivery study has been written and pretested, which will compare HTI prefilled and Tekpak user-filled applicators using hydroxyethyl cellulose (HEC) placebo.
- Prefilled applicators for the dose delivery study have been received through collaborations with CONRAD and the International Program on Microbicides. User-filled applicators are ordered.
- A report on international manufacturers has been finalized and is available for dissemination. The study includes findings on an applicator manufacturers search in India and South Africa.
- A presentation on HealthTech applicator activities was made at the Alliance for Microbicide Development meeting in March 2006. This resulted in "delivery methods" being incorporated into the Microbicide Development Strategy which can hopefully highlight the importance of this topic among key donors and stakeholders.

Problems encountered and actions taken to resolve them

- We were unsure of the appropriate multidose tube size to use for clinical study (of KY Jelly). After consulting with microbicide developers and researchers to get technical input, we assessed currently available tube sizes of KY Jelly and considered optimal multidose tube sizes for product introduction. Based on all factors, we decided to go with the tube holding 4 oz/124 ml of gel (approximately 35 doses at 3.5 ml/dose or 50 doses at 2.5 ml/dose).
- For the dosage delivery study, we need to repackage HEC placebo taken from surplus prefilled applicators so that it can be used for user-filled applicators. This requires technical testing and experimentation with packaging gel into aluminum multidose tubes to avoid air bubbles and other technical variations. This testing is currently underway and will not affect the study timeline.

Next steps and milestones expected in the next six months

- Three presentations on PATH applicator activities will be made at the Microbicides 2006 conference in Cape Town, South Africa, in April 2006, including at the general conference, a WHO-sponsored Southern Africa regulatory meeting, and the International Working Group Meeting.
- The clinical study will be submitted for review and approval by Human Subjects Review Committees at PATH and Profamilia. The study will be initiated, with data collection to be near completion by October 2006. The dose delivery study will be completed and those results made available.
- PATH/HealthTech will continue talks with microbicide sponsors who are interested in linking their microbicide with the user-filled applicator or other delivery devices (CONRAD, Population Council) and will prepare for the possible next round of studies in 2007 to evaluate microbicide products with alternative delivery devices.

Packaging Solutions to Improve Provision of Nevirapine in PMTCT Programs

Goals of project

The goal is to reduce mother-to-child transmission (MTCT) of HIV by improving antiretroviral therapy coverage in prevention of MTCT (PMTCT) programs through developing, evaluating, and facilitating introduction of improved single-dose packaging solutions for nevirapine (NVP).

Status of project as of March 2006

Technical development work on this project was completed in January 2006. The proposed packaging improvement is a self-sealing foil pouch designed to surround and protect the dispenser once the nurse fills it with NVP oral suspension (hereafter referred to as syrup). The pouch is also labeled with pictorial instructions as well as expiry information. A pilot introduction of this improved packaging began in Kenya in February 2006. Testing completed by Boehringer Ingleheim (BI) in late 2005 concluded that this packaging does not provide for any shelf life extension beyond BI's current two-month guideline for NVP syrup prefilled in an Exacta-Med®†† dispenser.

Achievements and progress in the past six months

- Technical development work on the foil pouch was completed in January 2006.
- BI's high performance liquid chromatography (HPLC) testing of NVP syrup prefilled in Exacta-Med dispensers and pouched was completed.
- The Kenya pilot introduction plan was written and approved by the National HIV/AIDS and STD Control program of Kenya (NASCOP).
- The pilot introduction started in February 2006. A total of 35 staff were trained, and NVP syrup is now being distributed in foil pouches in 13 clinics in 8 districts.

Problems encountered and actions taken to resolve them

- Results from HPLC studies conducted by BI concluded that shelf-life extension of NVP prefilled in an Exacta-Med dispenser is not feasible, although the foil pouch successfully prevented moisture loss.
- In consultation with USAID, the PATH team refocused project efforts around the pilot introduction in Kenya and wrap-up of all appropriate project design and development process documentation. Previously planned shelf life extension activities were cancelled, and approximately $75,000 was made available for reallocating to other HealthTech projects.

Next steps and milestones expected in the next six months

- The Kenya pilot introduction of the improved packaging for NVP will be completed and the report written.
- Documentation of the technical work to develop improved packaging will be completed.
- We will prepare and publish on the Web a NVP pouch sourcing manual to facilitate procurement of pouches.
- HealthTech will disseminate project results at the International AIDS Conference in Toronto.
- A stakeholders meeting in Kenya will be held to present findings from the pilot introduction and discuss next steps for broader introduction of the take-home approach.

†† Exacta-Med is a registered trademark of Baxa Corporation.

Strategic Objective 5

Rapid Diagnostics for Tuberculosis

Goals of project

The goals of this project are to:

- Develop or evaluate an accurate and simple test for tuberculosis (TB) that is affordable to populations in the developing world.
- Understand the need and market for rapid diagnostics for TB in order to make informed decisions about investments in development of tests.

Status of project as of March 2006

Development of a TB immunochromatographic strip (ICS) test has been discontinued due to poor results from field trials in Botswana, India, and Ukraine. PATH has started to evaluate the feasibility of a phage-based approach to a point-of-care test for tuberculosis. Meanwhile the study of the need and market for a rapid TB test is ongoing. Additionally, we are currently negotiating a collaborative arrangement with a private-sector company that is developing a TB diagnostic patch test. We are hopeful that this test will provide accurate diagnosis in resource-poor settings.

Achievements and progress in the past six months

- Negotiations are underway with Sequella, the maker of a promising TB patch test, to work together on a field evaluation of their technology in Ukraine. The test requires no instrumentation, can be stored at room temperature, can be read by nonexpert users, and has performed much better than smear microscopy in recent field trials in the developing world.
- PCR and culture validation methods to determine the concentration of the TB surrogate organism M. bovis BCG, as well as the TB-infecting phage DS6A, were developed as part of an effort to construct a rapid assay for TB as well as TB drug susceptibility based on phage amplification.

Problems encountered and actions take to resolve them

- In the initial stages of negotiation with Sequella, we had no project funds to cover costs of a collaborative field project. Funds originally allocated to the market study of TB diagnostics which USAID had commissioned were reallocated for this use. Also, we are discussing cofunding options with the PATH Ukraine office.
- For the work on a phage-based TB assay, we found that, contrary to evidence in the literature, DS6A does not sufficiently infect M. bovis BCG, an organism that can be handled in a BSL 2 laboratory. DS6A, however, does infect the ultimate target organism M. bovis BCG, but this work will require access to a BSL 3 laboratory. PATH has established a collaboration with a local partner, the Seattle Biomedical Research Institute (SBRI), with those facilities. Additional funds will be needed for this next step.

Next steps and milestones expected in the next six months

- A work plan and a kick-off meeting in Kiev, Ukraine, for the PATH/Sequella fieldwork, which will include a market study and field-based evaluation of optimal reagent dosing and performance, will be developed and carried out.
- The protocol for the dosing study will be written and submitted to the PATH and Ukraine local institutional review boards.
- Initial market study data collection will be completed.
- Further work on the TB phage as a signal transduction mechanism is likely to be carried out under a new NIH grant application to be submitted jointly with SBRI.