

HealthTech IV

Cooperative Agreement #GPH-A-00-01-00005-00

Semiannual Report
October 2007 – March 2008

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

Submitted by:
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Highlights and milestones of HealthTech projects during the past six months

- Progress towards the introduction of DMPA in Uniject included participation by PATH, BD, and Pfizer at the Women Deliver conference in London in October 2007 where conference participants were openly informed about Pfizer's commitment to make the product available in the coming few years.
- An on-line survey about current experiences from both the family planning field and the HIV/AIDS field with incorporating female condoms into promotion, programming, and advocacy was conducted among 206 participants from 44 countries. In addition, stakeholders were interviewed. The results will be useful in planning introduction of the devices into programs; one finding was that VCT (Voluntary Counseling and Testing) programs appear to be the "most feasible" area for expanding access.
- After an extensive review and evaluation of potential manufacturers for the Woman's Condom in China, HealthTech has selected a lead candidate and engaged in collecting additional information about that company as part of final due diligence. The research further confirmed the strength of Shanghai Dahua Medical Device Company as a suitable partner for this work. A letter of intent was shared with Dahua and a detailed work plan that outlines the steps of technology transfer and regulatory approval in China has been developed. This is a major step in the path of this product to being available on the market.
- A training video of three different no-scalpel vasectomy (NSV) procedures has been produced in India and edited in the United States to provide a basis for training materials for the upcoming randomized control trial (RCT) in India, to be managed by Family Health International and the Indian Council on Medical Research.
- After a multiyear period of no supply at all, oxytocin-Uniject is now again available, albeit on an initial limited basis, for use in field evaluations and pilot introduction efforts. BIOL (the Argentinean private-sector collaborator) can now supply oxytocin-Uniject for field studies and is on course to receive registration and marketing approval from the Argentine food and drug administration in the next period.
- In November, WHO published an aide-memoire for prevention of freeze damage to vaccines (http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.09_eng.pdf). This important policy document represents the culmination of years of HealthTech work to achieve official recognition of the damage to vaccines caused by exposure to freezing temperatures. This publication signals that the immunization community has accepted prevention of vaccine exposure to freezing temperatures as a global priority.
- HealthTech, in partnership with WHO and UNICEF, released version 1.0 of the Cold Chain Equipment Management (CCEM) Tool, both on CD and via the PATH website (<http://www.path.org/publications/details.php?i=1569>). This robust tool is designed to help strategically manage a national inventory of cold chain equipment by providing the framework for a comprehensive picture of current and future equipment needs. In the next phase, HealthTech will be refining the tool and creating a tutorial and training workshop to promote its use. It is anticipated that this tool will have rapid uptake among countries overhauling ailing cold chains and among those countries planning for the introduction of new vaccines. Several countries have already expressed interest in using CCEM for this purpose.
- The work to introduce needle removers as a viable health care waste management alternative in India in 2003 and that placed 31 needle removers in seven health facilities has been published in *Tropical Doctor* (Muller N, et al. Evaluating the use and acceptability of a needle-remover device in India. *Tropical Doctor*. 2007 Jul;37(3):133–135).
- A market assessment of existing neonatal resuscitation devices in the Southern African Development Community (SADC) has been completed and key recommendations shared informally with USAID.

The final report on the analysis of the essential newborn care in selected states in India is being published for distribution at an upcoming dissemination seminar in Delhi.

- To identify user preferences for the types of platforms and priority micronutrients that would be candidates for diagnostic tests, a needs assessment survey was posted on a SurveyMonkey website and invitations were sent to over 350 participants to respond. Over 60 individuals have responded to date, and the survey is being sent to clinicians to obtain input on the perceived usefulness of micronutrient point-of-care tests for the treatment of infectious diseases.
- A development and introduction plan for the chlorhexidine (CHX) product into Bangladesh has been drafted and is currently being implemented by all relevant parties. CHX product development and introduction activities in Nepal are currently on hold pending decision by USAID stakeholders.
- For the safe water test, HealthTech has completed culturing and performed testing on five platforms, including membrane filtration with culture on two separate media—MPN testing and the Petrifilm system. A final report on our activities was written and submitted to USAID. The finding concluded that it is possible to culture *E. coli* at temperatures from 22°C to 40°C. However, 45°C gave inconsistent results strain to strain. This would allow testing using some standard methods without use of an incubator to test for fecal contamination of drinking water supplies.
- With funding from the CDC National Vaccine Program, HealthTech and its partners have conducted a Phase 2 randomized controlled trial to assess the safety and immunogenicity of intradermal (ID) delivery of a licensed inactivated trivalent influenza vaccine of varying dosages in immunocompetent elders age 65 and over. The safety and immunogenicity of ID injection was compared to intramuscular (IM) delivery of influenza vaccine. One of the significant findings was that influenza vaccine at 60% dose by either IM or ID route achieved comparable antibody titer, and were similar to full dose IM vaccination among highly vaccinated, healthy elderly individuals.
- HealthTech has established a collaboration with a diagnostic company in India to provide an accurate and simple test for determining multi-drug resistant tuberculosis by using the microscopically observed drug susceptibility approach that is affordable and useful for populations in the developing world. The company is currently creating a first-generation prototype for a collaborative evaluation in India and possibly Peru.

Element: Family Planning/Reproductive Health

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 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 2008

Pfizer and BD are working closely on the various activities necessary for Pfizer to request United States Food and Drug Administration (USFDA) review and registration of DepoProvera SC in the Uniject device. Our current understanding based on February 2008 discussions with Pfizer is that this submission will not happen until sometime in 2009, with expected approval coming 12 months later in 2010.

Pfizer experienced delamination of the Uniject device plastic blisters in a small number of lots of the devices supplied by BD. BD reported that it has traced the problem to a specific, controllable cause and resolved the issue to the satisfaction of Pfizer.

Achievements and progress in the past six months

PATH, Pfizer, and BD had a presence at the Women Deliver conference in London in October 2007 and openly informed conference participants about Pfizer's commitment to make the product available in the coming few years. In coordination with USAID, Pfizer, and PATH, BD originally planned to seek major media attention for the collaboration and product as part of the Women Deliver conference but at the last minute had to curtail those plans. Pfizer had unfortunately become entangled in an unrelated but highly visible, highly charged, controversy surrounding some of its research practices in developing countries in early October 2007. Pfizer executives decided it was best to defer any announcements until the media climate was more neutral to positive.

Problems encountered and actions taken to resolve them

In early February 2008, Enrico Ligerri, the longtime project lead from Pfizer, informed PATH (Steve Brooke) that he would be taking a new assignment overseas within Pfizer starting in late Spring 2008. PATH requested an opportunity to meet with Mr. Ligerri before he left and to be introduced to whomever from Pfizer would be taking over, in particular, the business and marketing planning functions for the product. Mr. Ligerri was not available to meet and stated that for the time being he would continue to play this role.

Next steps and milestones expected in the next six months

- Schedule and hold a partners' meeting to include BD, Pfizer, USAID, and PATH. It is particularly important to establish broader relationships with various involved Pfizer staff now that Pfizer's longtime project lead, Enrico Ligerri, is moving overseas for a new position within Pfizer.
- Contingent on agreement on timing by all partners (Pfizer, BD, USAID and PATH), PATH's media relations staff are ready to develop and implement efforts to gain positive media attention for this project and product.

* Uniject is a trademark of BD.

Vasectomy technologies

Goals of project

Under this project, HealthTech aims to:

- Develop text and video materials to train vasectomy surgeons in India no-scalpel vasectomy (NSV) as part of a randomized control trial (RCT) in India of a no-scalpel vasectomy (NSV) managed by Family Health International and Indian Council on Medical Research.

Status of project as of March 2008

A training video of three different NSV procedures has been produced in India and edited in the United States (US) to provide a basis for the video training materials for the upcoming RCT. PATH is now adapting a text guide on NSV procedures to use as a text-based training guide for physicians who will perform vasectomies in the RCT.

Achievements and progress in the past six months

- A video firm in India collaborated with the chairman of the NSV Surgeons of India to film three NSV methods for creation of training video for a RCT on three no-scalpel vasectomy NSV methods. (October 2007–February 2008).
- A Seattle-based video editor added appropriate text including titles and credits.
- Four external reviewers recommended by the principal investigators for the RCT trial are reviewing the three surgical techniques that are being proposed as the standard techniques for the trial to note their agreement/disagreement as to the chosen techniques.
- PATH has initiated the first draft of the RCT training guide for use in training physicians performing vasectomies.

Problems encountered and actions taken to resolve them

- Development of the written training material has been delayed due to staff changes. A former PATH technical officer now consultant, Yancy Seamans, has now been engaged as a consultant to manage this task.

Next steps and milestones expected in the next six months

- In the coming months, the training video will be finalized and sent to the principal investigators for the RCT trial. PATH will also finalize the training guide text and circulate it to reviewers in anticipation of having the RCT trial start in June.

Advancement of female barriers

Goals of project

Under this project, HealthTech seeks to characterize the status regarding promotion of and access to female barrier methods through HIV-prevention programs and identify opportunities and strategies for expanding access to female barrier methods. Although this research focused on female condoms (the only female-initiated prevention technology currently available), the goal is to seek lessons and strategies to help prepare the way for other barrier methods, such as the SILCS Diaphragm and/or microbicides, when they become available.

Status of project as of March 2008

This project consisted of three main activities. The first included background research and stakeholder interviews to assess the current experiences from both the family planning field and the HIV/AIDS field with incorporating female condoms into promotion, programming, and advocacy. Next we developed and implemented a web-based survey to obtain feedback from a range of participants about their attitudes and experience incorporating female condoms into health programming. Lastly, we analyzed the study results, drafted the final report, and are seeking opportunities to share study findings in national and international venues.

Achievements and progress in the past six months

- The on-line survey was closed in November 2007, after being open for three months. In total, more than 206 participants from 44 countries completed a part of the survey and 148 participants completed the entire survey.
- Our background research was successful in identifying individuals from both the family planning and HIV/AIDS fields to participate. Almost 60 percent of study respondents reported working primarily in the HIV/AIDS field during the past five years.
- Data analysis began in December 2007 and continued through March 2008.
- Key findings and recommendations have been drafted and submitted to several international meetings.
- A final report of the survey results is being completed. Selected findings include:
 - While most respondents were strong proponents of integrating female condoms into HIV/AIDS prevention and treatment programs, most reported a lack of institutional support for this effort.
 - A majority of respondents believed that female condom promotion results in a positive health impact even though few could report primary indicators used to measure success of integrating female condoms into prevention and treatment programs.
 - Opportunities exist where female condoms can be integrated into prevention and treatment programs. A majority of respondents identified VCT (Voluntary Counseling and Testing) programs as being the “most feasible” area for expanding access and PMTCT (Prevention of mother-to-child transmission) programs as the “least feasible.”
 - Four of the top five barriers to large-scale integration of female condoms related to gaps in the health system. Almost half of the respondents rated lack of donor support for large-scale efforts as “very significant.”
 - While a majority of respondents “agreed” or “strongly agreed” that cost of female condom was *the major barrier* to program integration, almost a third of those respondents identified other barriers such as poor user acceptability of the existing product, negative provider perception, lack of donor/government commitment, and cultural perspectives relating to barrier method use as playing an important role in limited program access.
- In part due to this web survey, PATH was invited by the Implementing Best Practices (IBP) Community to facilitate an on-line discussion about female condoms in April 2008 to help publicize

the new source book, *Family Planning: A Handbook for Providers*. The background research and survey findings have been instrumental in shaping this discussion.

Problems encountered and actions taken to resolve them

We have experienced difficulty finding the appropriate venue to share study findings. Abstracts submitted to two international conferences (Women Deliver and Global Health Council) in Fall 2007 were not accepted. We subsequently submitted an abstract to the American Public Health Association annual meeting and are awaiting results.

Next steps and milestones expected in the next six months

- Complete data analysis and finalize report of key findings.
- Seek opportunities to share study findings or use findings to stimulate dialogue with key stakeholders.
- Identify non-governmental organizations (NGOs) or programs that are most responsive to expanding access to female condoms and assess opportunities for implementing key recommendations with these programs.

Advancement of woman's condom—commercialization

Goals of project

Commercialization activities conducted in 2006 had identified a number of potential commercial partners in China and India who were interested in manufacturing or distributing the PATH Woman's Condom. The goal of this project is to complete due diligence and final selection of partner(s) to which the technology can be transferred for good manufacturing practices production of the device. Parallel to this work, PATH will continue to identify a pathway forward for regulatory approval and market access.

Status of project as of March 2008

As of March 2008, we have expended the funds provided by HealthTech. We have completed the due diligence and selection process for evaluating the manufacturing candidates in China and India, and we have selected a first-choice candidate. With other funding, we are in the process of negotiating a commercial agreement with this manufacturing partner.

Achievements and progress in the past six months

- In collaboration with a manufacturing and technology transfer consultant, and with PATH staff in China and India, the research conducted in 2006 was reviewed and a short list of manufacturers identified with whom PATH arranged on-site visits and factory tours.
- In September and October 2007, our consultant visited five manufacturers in China and six companies in India. In China, he was accompanied by China PATH staff. The goal of the trip was engage manufacturers in discussions to determine interest and commitment and to evaluate the technical and manufacturing capability of each candidate to determine their appropriateness and chances for success as a commercial partner for Woman's Condom production.
- After the site visits, gathered data was reviewed with the Woman's Condom team in Seattle, and the choice was narrowed to three manufacturers—two in China and one in India. A list of technical, regulatory, and marketing criteria were developed, and requests for further information were sent to each of the three candidates, along with a package of information designed to let each manufacturer know more about the specifics of the condom design and materials, to help them in answering our request. Two of the three manufacturers responded to the request.
- Based on the information provided by each manufacturer, PATH chose a lead candidate and engaged in collecting additional information about that company as part of final due diligence. The research further confirmed the strength of Shanghai Dahua Medical Device Company as a suitable partner for this work. A letter of intent was shared with Dahua and we developed a detailed work plan together that outlines the steps of technology transfer and regulatory approval in China.

Problems encountered and actions taken to resolve them

- Sufficient funding has been lacking to move confidently into the technology transfer stage. We are currently pursuing funding opportunities with three potential donors, including USAID.
- As a result, internal human resources dedicated to this project have been limited. We are currently accessing business consultants in order to help fill the gaps, and hiring is underway.

Next steps and milestones expected in the next six months

- The funding for this project under the USAID Family Planning/Reproductive Health account as been expended. We are currently waiting for a decision on a request for funding made through the Microbicide account that would begin in July 2008 and would allow us to proceed with technology transfer of the manufacturing process to our chosen manufacturing partner.

Exploring cost reduction of levonorgestrel-releasing IUD

Goals of project

The goal of this project will be to assess opportunities for expanding access to a levonorgestrel-releasing IUD by investigating the potential for expanded access to the existing product. This will be done by characterizing efforts to develop and bring to market a lower-cost version of a hormonal IUD and working with stakeholders to clarify the commitment required to bring a lower-cost therapeutic IUD to market. This project fits within the goal of expanding access to underutilized reproductive health technologies.

Status of project as of March 2008

Project funding started in November 2007. Initial-stage research identified either proposed or currently on-going IUD initiatives being undertaken by entities external to PATH that suggested the need to modify the project scope of work. In response, the scope of work was revised to center around conducting an updated landscape analysis using a report outlining opportunities for a levonorgestrel-releasing IUD that was recently released by the Hewlett Foundation[†] as a basis.

In follow-up to this report, we are interviewing IUD stakeholders to assess their reactions to the options and recommendations outlined and to explore the degree of political and technical commitment necessary to implement the report recommendations. An additional activity to investigate the Chilean manufacturer (Laboratorios Alpha) which is developing a hormone-releasing IUD, will be added to the current scope of work.

Achievements and progress in the past six months

- Background research was initiated; project scope of work was refined based on new inputs.
- Contact has been made with the Chilean manufacturer, Laboratorios Alpha. Preliminary investigation of progress on their hormone-releasing IUD initiated.
- Key stakeholders have been interviewed to assess reactions and commitment to the various strategies for a lower-cost levonorgestrel-releasing IUD outlined in the Hewlett report and to assess donor commitment to any of the identified strategies.

Problems encountered and actions taken to resolve them

- Initial investigation into this topical area documented that other organizations had already identified strategies to lower the cost of a levonorgestrel-releasing IUD. Based on this information, the scope of work and project strategy was refined to avoid duplication with previous efforts.

Next steps and milestones expected in the next six months

- Efforts to develop a hormone-releasing IUD at Laboratorios Alpha will be characterized, including technical capacity and a regulatory plan.
- Interviews with stakeholders to characterize assessment of the various strategies and commitments to bringing a hormone-releasing IUD to market given other competing demands will be completed.

[†] Pollack AE, Ross J, Perkin G. *Intrauterine devices (IUDs) in developing countries: Assessing opportunities for expanding access and use*. Available at: <http://www.hewlett.org/NR/rdonlyres/02DF606B-4918-4504-A55F-D71C9BC932B4/0/IUD.pdf>.

- HealthTech will develop a summary of the various strategies and initiatives planned or underway and characterize the relative advantages of each.
- HealthTech will share the updated analysis with donors and other key stakeholders, possibly through a short consultation or other means, to determine which (if any) of these strategies are sufficient to meet donor and public health goals at this time.

Element: Maternal and Child Health

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 thereby 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 2008

After a multiyear period of no supply at all, oxytocin-Uniject is now again available, albeit on an initial limited basis, for use in field evaluations and pilot introduction efforts. BIOL (the Argentinean private-sector collaborator) can now supply oxytocin-Uniject for field studies and is on course to receive registration and marketing approval from the Argentine food and drug administration (FDA) in the next period. A second potential supplier, Gland Pharma of India, continues active development of its oxytocin-Uniject product. This progress on the “supply side” has helped to support increasing interest and activity on the “demand side.” A growing number of field studies—targeting over ten countries so far—are in various stages of active planning and preparation.

Achievements and progress in the past six months

- HealthTech is now in active contact with WHO regarding supply of BIOL’s oxytocin-Uniject for the WHO multi-country trial on components of AMTSL. The countries involved are Argentina, Egypt, India, Kenya, Philippines, South Africa, Thailand, and Uganda. WHO will require 30,000 doses by late summer/early fall 2008 and is willing to reimburse BIOL for production expenses. As long as no unanticipated hurdles emerge from either side, we are confident this will be a successful use of BIOL’s oxytocin-Uniject in a critical WHO study.
- Stability study results for BIOL’s oxytocin-Uniject continue to be quite positive, having passed the 24-month time point. Product stability is at the upper end of the range relative to other manufacturers’ oxytocin injection United States Pharmacopeia (USP) products, based on information available to PATH.
- HealthTech staff visited Gland Pharma in India on December 4, 2007, leveraging off of travel for other projects. The objectives of the meeting were to receive an update on Gland Pharma’s progress with oxytocin-Uniject and educate the Gland team regarding time-temperature indicators (TTIs), to help get TTI “on the Gland agenda.” Gland appreciated the potential for TTI’s to add value to their prospective oxytocin-Uniject product. Gland also identified technical issues that have delayed development of their product (see also actions taken).
- HealthTech and the Prevention of Post Partum Hemorrhage Initiative (POPPHI) jointly hosted a meeting between Gland, BD India, Indian Council of Medical Research (ICMR), and PATH staff located in India, at PATH’s office in Delhi on November 1, 2007. This meeting was held to clarify expected timelines, next steps, and necessary coordination regarding Indian/ICMR evaluation of oxytocin-Uniject.

Problems encountered and actions taken to resolve them

- The study of oxytocin-Uniject in Argentina began with preliminary trainings and site work. Actual first introduction and use of the BIOL oxytocin-Uniject is on hold pending issuance of registration by the Argentine FDA, which is anticipated to come at anytime between now and October 2008. BIOL

[‡] Uniject is a trademark of BD.

has committed to supply product for the study either from its current (limited) inventory or if necessary from a new production batch.

- Gland Pharma encountered technical issues, and its timeline for initiation of formal stability studies slipped, but Gland leadership remains committed to the project. Following December meetings with Gland, HealthTech and BD developed a technical assistance plan. A HealthTech technical consultant will visit Gland in April 2008 to help them move forward.
- While two pharmaceutical companies are now actively pursuing registration of their oxytocin products in the Uniject device, both are still operating in a pilot-scale production mode. The companies are hesitant to invest in full production scale-up until there is more direct, concrete evidence that either donors or country governments will be willing to pay an increased price for the convenience and benefits of oxytocin-Uniject when compared to oxytocin in ampoules, which sell for extremely low prices of close to US\$0.10 per dose.
- As always, there are risks that the regulatory agencies will delay their approvals. BIOL originally estimated that it would receive approval from ANMAT, the Argentine FDA equivalent, by early 2008. (BIOL submitted the application in August 2007.) Unfortunately, ANMAT has moved slower than expected. ANMAT's process has seven steps, and to date BIOL's application has progressed through six of those. Along the way, BIOL has responded promptly to routine technical questions from the ANMAT reviewers. BIOL now estimates approval will be forthcoming at any time between now and October 2008, at the latest.

Next steps and milestones expected in the next six months

- BIOL will provide supply for an operational research study of oxytocin-Uniject in South Africa that is being implemented by PATH's office in South Africa (co-funding is supporting all aspects of the study including the supply of oxytocin-Uniject by BIOL). Planning of this study has encountered unrelated delays—originally we had anticipated requiring product earlier, although BIOL should be able to provide product when needed. It is worth noting that although this is an operational research study, the South African authorities will consider it a clinical research study and the oxytocin-Uniject an investigational product since oxytocin-Uniject is not registered (i.e., does not have marketing approval) in South Africa. This is a logical position for national authorities to take and is in line with best practices of agencies such as the United States Food and Drug Administration (USFDA). PATH's office in South Africa is retaining a contract research organization with in-country regulatory expertise to help facilitate study and product importation approvals.
- BIOL will obtain registration of its oxytocin-Uniject in Argentina, currently expected at any time and no later than October 2008.
- Gland Pharma, BD, and HealthTech will develop an updated timeline for development of Gland's oxytocin-Uniject product as part of the technical assistance visit planned for April. A separate update will be shared at that time.

Immunization and delivery technologies

Goals of project

The project goal is to strengthen immunization delivery systems by advancing technologies, policies, and practices that ensure proper handling of vaccine during transport and storage and that protect health workers and communities from medical transmission of disease through unsafe injection practices. To achieve this goal, the team will:

- Facilitate the development and introduction of new technologies for vaccine refrigeration, cold chain temperature monitoring, safe injection, and health care waste management (HCWM).
- Build global policy supporting best practices in HCWM, injection safety, and vaccine management.
- Assist in strengthening cold chain capacity in preparation for the introduction of new vaccines.
- Assist in strengthening HCWM systems for managing medical waste.

Status of project as of March 2008

As new vaccines, presentation formats, and technologies are introduced, developing-country health systems that are already strained under their current Expanded Programme on Immunization (EPI) load are at risk of failure. PATH continues to lead the global movement to identify approaches to strengthen vaccine delivery systems and introduce solutions to manage the associated waste. Recent collaborations with other non-governmental organizations (NGOs) such as Healthcare Without Harm and John Snow Inc., as well as with other PATH teams addressing immunization delivery logistics issues, have enabled the leveraging of HealthTech resources to maximize impact.

HealthTech expertise in the area of cold chain and vaccine delivery logistics has also been leveraged through a new WHO-PATH collaborative project, Optimize—Immunization Systems and Technologies for Tomorrow. This project comprises immunization logistics experts from WHO and PATH and includes members of the HealthTech immunization teams. The Optimize project is focused on systems, and is directed toward developing a shared vision of the future of global immunization. It will be up to HealthTech and other parties to implement the concrete steps toward realizing the resulting vision. HealthTech remains PATH's primary source of funds for technology-related work, and provides critical and nonredundant funding that will continue to enable PATH to evaluate the need; assess technical feasibility; and advance, if appropriate, technologies that improve the safety and/or effectiveness of immunization in developing-country settings.

Achievements and progress in the past six months

- HealthTech, in partnership with WHO and UNICEF, released version 1.0 of the Cold Chain Equipment Management (CCEM) Tool, both on CD and via the PATH website (<http://www.path.org/publications/details.php?i=1569>). This robust tool is designed to help strategically manage a national inventory of cold chain equipment by providing the framework for a comprehensive picture of current and future equipment needs. In the next phase, HealthTech will be refining the tool and creating a tutorial and training workshop to promote its use. It is anticipated that this tool will have rapid uptake among countries overhauling ailing cold chains and among those countries planning for the introduction of new vaccines. Several countries have already expressed interest in using CCEM for this purpose.
- Increased awareness of the widespread exposure of vaccine to freezing temperatures has spurred interest in expanding the range of freeze indicators available to country immunization programs. In response, HealthTech is supporting activities to evaluate some new freeze indicators that could be appropriate for low- and middle-income immunization programs. The team has completed planning and preparation of a study to be carried out in Indonesia in second quarter 2008 to collect feedback from cold chain decision-makers and end users regarding the acceptability, performance, costs, ease of use, and system-fit of three prototype freeze indicators and a radio frequency identification (RFID) temperature monitor.

- In November, WHO published an aide-memoire for prevention of freeze damage to vaccines (http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.09_eng.pdf). This important policy document represents the culmination of years of HealthTech work to achieve official recognition of the damage to vaccines caused by exposure to freezing temperatures. This publication signals that the immunization community has accepted prevention of vaccine exposure to freezing temperatures as a global priority.
- In January, WHO asked PATH to complete the verification test protocol for the Performance, Quality, and Safety (PQS) standard for needle removers. Completion of this protocol in the second quarter of 2008 will be followed by review and publication of the standard for needle removers, likely before the end of the year. This is an important step in WHO's acceptance of this technology that PATH through HealthTech has been advancing and advocating for a number of years in order to help manage the most dangerous element of health care waste—infectious sharps.
- HealthTech has identified two manufacturers who have interest in exploring the possibility of producing the “needle plug and scissors” or “Hopkins” needle remover design developed under HealthTech several years ago. This is a low-cost needle-remover design that fits on a container provided by the user and allows removal of needles into this container for later safe disposal.
- The work to introduce needle removers as a viable HCWM alternative in India in 2003 and that placed 31 needle removers in seven health facilities has been published in *Tropical Doctor* (Muller N, et al. Evaluating the use and acceptability of a needle-remover device in India. *Tropical Doctor*. 2007 Jul;37(3):133–135).
- PATH is bench testing a new plastic-spike reconstitution syringe design and has facilitated the transfer of 1,000 prototype syringes for WHO to use in an upcoming trial of aerosolized measles vaccine in the third quarter 2008. By incorporating the plastic-spike reconstitution syringe into this evaluation, the entire process will be rendered needle free. The implications of this application of needle-replacing technology could be far reaching.
- HealthTech is continuing to explore alternative options to the incineration of medical waste, which can create health problems for health workers and communities. HealthTech provided design feedback on a prototype syringe melter in 2007, and staff provided technical assistance during a second field evaluation of the revised design in the first quarter of 2008. In addition, leveraging PATH's work in Botswana through the Making Medical Injections Safer (MMIS) Project, HealthTech staff continue to assist Botswana through a collaboration with Health Care Without Harm, MMIS, and several government partners to identify and select an appropriate technology for treating infectious waste that does not use incineration.
- HealthTech expertise in development and introduction to injection safety technology is recognized among injection safety advocates. This is evidenced by HealthTech staff's advisory role to UNICEF within the context of a committee of experts providing input on the design and implementation of an evaluation of reuse prevention syringes for vaccine reconstitution.

Problems encountered and actions taken to resolve them

- HealthTech has provided assistance to the Japanese refrigerator manufacturer, Twinbird, in the development of their vaccine refrigerator with the intent of pursuing WHO prequalification. However, as we finished development and began the process of pretesting according to the PQS standard, it became clear that the Twinbird technology does not fit well in any of the existing PQS categories. The main issue is the use of a battery to provide the required holdover period (during power outage). We now find ourselves in the difficult position of requiring either a WHO exception to the standard or the development of a new standard category. PATH remains committed to finding a solution and helping to ensure that innovative technologies will have access to the PQS system and thus to procurement for developing-country immunization programs.
- HealthTech staff have provided technical assistance to the Peru MOH in drafting a report on the retractable syringe evaluation that was completed in October 2006. However, a natural disaster in Peru, communication barriers, and work overload caused lengthy delays. HealthTech staff have

offered assistance to UNICEF and the Peru Ministry of Health (MOH) to help complete the manuscript and are in the process of finalizing it in English. Once complete, the manuscript will be sent to UNICEF and the Peru MOH for translation and publication.

- The schedule for the WHO aerosolized measles trials continues to be delayed. Because the evaluation of the plastic spike depends on the scheduling of this study, the exact date for implementation remains unclear.
- In Botswana, communication challenges involving multiple government partners combined with existing contracts to purchase incinerators have delayed the selection process of non-incineration technology. There is also a concern about committing funding to a new, unknown technology approach. The team is working with colleagues in Botswana to locate a private hospital that may be interested in helping to identify an alternative approach to treating its waste. This option could allow the government to increase their awareness and comfort level by participating in the decision-making process and understanding the benefits and risks for various approaches without having to make a commitment themselves.

Next steps and milestones expected in the next six months

- A CCEM Tool tutorial and training workshop will be developed and piloted in at least one additional country.
- A report on the Indonesian field evaluation of three freeze indicators and an RFID temperature monitor will be completed and disseminated globally. HealthTech will work with the manufacturers to identify next steps and opportunities for introduction of the technologies.
- The team will connect with WHO on the adaptation of the PQS specifications to accommodate a broader range of freeze indicator technologies and to accommodate new, nontraditional refrigeration technologies, and will assist WHO in moving towards the finalization of specifications and a verification protocol for needle removers.
- A marketing package on the SolarChill vaccine refrigerator will be released in the second quarter of 2008. It is anticipated that SolarChill will complete the PQS process and achieve WHO prequalification status within this period as well.
- The team will support UNICEF and the Peru MOH with the completion of the final report on the evaluation of the retractable syringe introduction which will be disseminated globally.
- The team will complete bench testing of several needlestick-prevention syringes and provide feedback to manufacturers to refine ideas for developing-country use. A field evaluation will be planned to evaluate use and acceptability of one to three specific syringes within a service delivery setting.
- A case study documenting the HCWM technology decision-making process in Botswana will be drafted as a means of facilitating the process in other countries.
- The HealthTech team will continue to work with two manufacturers on the possibility of commercializing a low-cost needle-remover device developed previously by PATH.
- HealthTech will work to identify developing-country safety box manufacturers or manufacturers with the capacity to produce safety boxes and will provide technical assistance to improve materials and manufacturing processes. The target of this work is a WHO-approved, lower-cost safety box.
- HealthTech will collect user feedback on plastic-spike reconstitution syringe during WHO aerosolized measles vaccine trial.
- We will also draft a report on acceptability and ease of use of reconstitution syringe and provide technical assistance with design modifications.

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”) and to fully evaluate this innovative combination for use in the treatment of neonatal infections.

Status of project as of March 2008

BIOL of Argentina has produced gentamicin-Uniject to supply the Nepal Family Health Project (NFHP) evaluation in Nepal and will complete final packaging and shipment as soon as all required approvals in Nepal are granted. HealthTech and BIOL are working to develop and compile the data and expert opinion support for a submission by BIOL for Argentine FDA registration of gentamicin-Uniject. Field evaluation of gentamicin-Uniject in Nepal is on hold pending final approval from Nepalese authorities.

Achievements and progress in the past six months

- The proposal to field test gentamicin-Uniject in Nepal is undergoing review and approval by Nepalese authorities. Questions posed by the Nepal Health Research Council relating to the field evaluation were successfully addressed by Steve Hodgins at NFHP.
- HealthTech initiated exploration of the option presented by Abhay Bang of the Society for Education Action and Research in Community Health (SEARCH) to use his India site for a cross-over comparison of syringe and needle versus gentamicin-Uniject. Mr. Bang is scaling up a newborn care package to sites for Maharashtra state (urban, rural, and tribal) to replicate the SEARCH newborn care model. Mr. Bang said the health workers would be ready to implement sepsis management in about nine months (summer 2008).

Next steps and milestones expected in the next six months

- HealthTech will commission or facilitate expert drafting of a paper summarizing rationale and justification for the specific dosing indications for registration of gentamicin-Uniject. This will enable BIOL to complete regulatory documentation necessary for their application to the Argentine FDA for registration of gentamicin-Uniject, a key step on the path to eventual commercial availability.
- BIOL will continue to complete stability studies, and to finalize and submit registration dossier.
- HealthTech and BIOL will document resolution of critical technical feasibility issues for gentamicin-Uniject by submitting manuscript on compatibility/stability test results of the gentamicin-Uniject product for publication in a peer-reviewed journal.
- We will monitor ongoing community-based studies designed to reduce neonatal mortality.
- HealthTech will also monitor the international policy debate regarding possible change in standard treatment guidelines for neonatal sepsis (i.e., inclusion of oral antibiotic with gentamicin-Uniject, “switch” therapy).
- We will engage key stakeholders in consultative meeting to discuss current data on sepsis treatment and its application to the value proposition for gentamicin-Uniject.
- We also plan to develop guidance for most appropriate scenarios/settings for using the gentamicin-Uniject product.
- We will continue to monitor progress of the MOH approval process in Nepal.

§ Uniject is a trademark of BD.

- If approvals are granted by the end of June, then HealthTech and NFHP/Morang Innovative Neonatal Intervention (MINI) will submit the protocol to ethical review bodies for approval and initiate the study (training completed, data collection underway).
- HealthTech staff will participate in coordination of the proposed second-stage field evaluation in Nepal.
- BIOL will complete production of the clinical trial lot of gentamicin-Uniject to meet the needs of field studies requiring product in the 2007 to 2008 time frame. As of today, all production steps except for final packaging have been completed. This will be done once Nepali authorities issue approvals for the study as well as importation and regulatory approvals.
- HealthTech will assist BIOL in developing a brief on a manufacturing scenario for the supply and cost of production for gentamicin-Uniject—including preparation of options and recommendations for economical and rational production scale-up.
- If MOH approval is not granted in Nepal by the end of June 2008, then we will begin to identify alternative site in collaboration with key stakeholders.

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 2008

Market assessment of existing resuscitation devices in the Southern African Development Community (SADC) has been completed and key recommendations shared informally with USAID. The final report on the analysis of the essential newborn care in selected states in India is being published for distribution at an upcoming dissemination seminar in Delhi.

Achievements and progress in the past six months

- The report from a situational analysis of essential newborn care in selected states in India conducted in collaboration with the Government of India (GoI), USAID/India, WHO-India office, UNICEF, IndiaCLEN, and PATH's office in India was finalized and a draft sent to USAID. A dissemination seminar for the India situational analysis report is being planned (tentatively set for summer 2008). A final report is being prepared for publication (100 copies) and distribution to key Indian stakeholders at the dissemination meeting.
- A market assessment of existing resuscitation devices in SADC countries and South Africa in particular was completed by the South African market research company Evolutions Research Solutions. The market research was leveraged from co-funding for a project in South Africa to strengthen newborn and maternal health systems and provides baseline information regarding availability, affordability, and use of current products in the 14 SADC countries as well as current and potential future market for these devices in the region. A report on the findings is in process and will be sent to USAID soon.
- A manuscript on the context-of-use survey was published by the *Journal of Tropical Pediatrics* as a research brief.
- A brief literature review and synopsis related to the use, preferences, and function of 240-ml vs. 500-ml bag sizes for resuscitation devices was completed in order to encourage UNICEF to include low-cost, high-quality devices in their catalog.

Problems encountered and actions taken to resolve them

- Dialogue with UNICEF regarding inclusion of a low-cost, high-quality device is stalled due to non-response from UNICEF colleagues. To address this, an in-house meeting will be conducted in April 2008 to brainstorm about alternative advocacy strategies for approaching UNICEF.

Next steps and milestones expected in the next six months

- HealthTech will refine a strategy for encouraging UNICEF to include affordable, high-quality devices in their catalog and disseminate to UNICEF stakeholders a literature review related to bag size.
- We will disseminate to key stakeholders a summary of results and recommendations from the market assessment in SADC countries.
- We will draft and submit to USAID for comment a strategy for enhancing availability of devices in the SADC region.
- A decision will be made regarding the next region (Economic Community of West African States [ECOWAS] or Eastern African) for market research and focus country/countries and we will identify a collaborating partner for participatory device evaluation in the same region as the market research.
- We will select a market research firm in at least one other region (ECOWAS or Eastern African) through an RFP process to implement a similar study protocol as the SADC study.

- HealthTech will also evaluate a device in a participatory study with potential users in the same region as the market research with draft results and recommendations expected by the end of December 2008 or earlier.
- Market research firms in at least one other region will conduct market studies with draft results and recommendations expected by the end of December 2008 or earlier.
- HealthTech will edit and submit manuscripts on the Indonesia asphyxia study that was conducted under other funding and which HealthTech is assisting with getting the results published in *Pediatrics*.
- We will also prepare and submit a manuscript to an appropriate journal on the essential newborn care study in India.

Rapid diagnostic test for newborn sepsis

Goals of project

The goals of this project are to provide an initial landscape analysis of the need for management diagnosis of neonatal sepsis in low-resource settings and of the opportunities for existing and emerging diagnostic technologies to address these needs.

Status of project as of March 2008

This project is on hold following submission of the final landscape analysis report and pending guidance from USAID regarding the outcomes of their newborn sepsis consultation held at the end of September 2007 to determine the next steps, if any.

Achievements and progress in the past six months

- None.

Problems encountered and actions taken to resolve them

- None.

Next steps and milestones expected in the next six months

To be determined in consultation with USAID.

Chlorhexidine for umbilical cord care

Goals of project

The goals of this project are to make an appropriate and affordable chlorhexidine (CHX) product for cleansing umbilical cords available in Nepal and to apply lessons learned in Nepal worldwide through the creation of a production development tool.

Status of project as of March 2008

A development and introduction plan of the CHX product into Bangladesh has been drafted and is currently being implemented by all relevant parties. CHX product development and introduction activities in Nepal are currently on hold pending decision by USAID stakeholders.

Achievements and progress in the past six months

- The final report of the Nepal-based manufacturer candidates including recommendation of most suitable partner was completed and disseminated to USAID.
- A final report of the United States Food and Drug Administration (USFDA) CHX landscape analysis was submitted to USAID at the end of October 2007.
- A joint site visit with PATH, Johns Hopkins University (JHU), and USAID to Bangladesh was conducted in February 2008.
- PATH completed collaborative plans with JHU to develop and roll out a CHX product in Bangladesh which included determining the feasibility of pilot testing a small run of lotion product.
- A scope of work (SOW) for Research, Training and Management International (RTM International) was developed and sent to USAID for comments. Follow up will be conducted with RTM via teleconference to confirm the SOW and negotiate an ongoing subagreement.
- Criteria were developed for selecting a local manufacturer in Bangladesh.
- A short list of manufacturer candidates in Bangladesh was created.
- The list consists of 14 pharmaceutical companies in Bangladesh, including the top ten manufacturers in terms of revenue and four other manufacturers identified by the report that RTM International developed (“Assessment of the commercial private sector for health care products in Bangladesh”). A manufacturing proposal that includes market information, such as top-level demand projection and target market segments, was developed for Bangladesh.
- A proposal was sent to the short list of manufacturers in Bangladesh to solicit their response/interest. Four companies (Beximco Pharmaceuticals, Acme Laboratories, Eskayef Bangladesh, and Popular Pharmaceutical) expressed their interest.
- A list of potential marketing research partners in Bangladesh was created.
- A SOW for a product attribute study in Bangladesh was developed. The RFP process for selecting a market research firm for this study in Sylhet was implemented. Two out of five companies that were sent the RFP responded with EOI. Only one of these companies responded with a detailed proposal (i.e., study design, cost estimate, etc.). A subcontract is currently being negotiated with that firm.
- Scopes of work were developed for SSFP (Smiling Sun Franchise Program) and SMC (Social Marketing Company) and both were sent to USAID for comments. The SOWs identified how these two projects might contribute to the global rollout of a CHX product in Bangladesh.

Problems encountered and actions taken to resolve them

- Progress on development of a CHX product for Nepal has stalled due to the lack of resolution between USAID/Global and the mission regarding an appropriate strategy. To address this, HealthTech has provided input whenever requested.

Next steps and milestones expected in the next six months

In Bangladesh

- We will select and negotiate a subcontract with a manufacturer for a CHX product in Bangladesh.
- HealthTech will transfer product specifications and provide technical assistance if required. The company will be asked to produce a CHX product for operations research (OR) incorporating the results from a product attribute study.
- HealthTech will engage with Johnson & Johnson (J&J) to assess their level of interest in providing support to this project and identify the areas where their support will be most effective.
- For the product attribute study, we will work with the selected market research firm to conduct the study in Sylhet. The results of the study will be disseminated to partners and a selected manufacturer (by end of July).
- HealthTech will visit Bangladesh in April/May 2008 and again in June to follow up with top candidates for a manufacturing partner and the market research partner, and with RTM International. We will meet with Center for Health and Population Research of Bangladesh (ICDDR-B) to follow up on their progress in the trial and preparation for an OR study. We will also visit Sylhet to observe the trial and identify any issues associated with production and packaging of the product.
- We also plan to interact with Bangladesh Rural Advancement Committee (BRAC) and confirm how to incorporate CHX product introduction into the safe delivery kit for the OR study.
- We will follow-up with the mission regarding the roles of SFP and SMC, as appropriate.

In Nepal

- In consultation with the Nepal Family Health Project (NFHP) and USAID, we will select the appropriate Nepal-based manufacturer negotiate SOW. We will discuss and finalize the agreement related to the transfer of the product specifications, and provide technical assistance if required.
- HealthTech will recommend appropriate India-based CHX bulk manufacturer(s) to the selected Nepal-based manufacturer if they need assistance for supplier selection.
- We plan to follow up with Anne Peniston, Senior Health Advisor, Office of Health and Family Planning at USAID/Nepal, as appropriate. We will participate in teleconference regarding the appropriate dose regimen for CHX product, if necessary.
- HealthTech will collaboratively write a development and introduction plan for the CHX product in Nepal with AED and NFHP, as appropriate. as well as coordinate with JHU to pilot test a small run of lotion product in Nepal, as appropriate.

Global

- HealthTech will continue a desk review of the experience and challenges faced by products such as oral rehydration salts (ORS) and zinc supplementation. All three products (CHX, ORS, and zinc) are composed of relatively inexpensive and readily available active ingredients, yet two of the three (ORS and zinc) have faced significant challenges in generating global demand and sustained markets. This experience can provide important lessons for the rollout of a CHX product.

Retinol binding protein enzyme immunoassay

Goals of project

The goal is to enhance the reliability and ease of assessment of vitamin A deficiency (VAD) 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 2008

HealthTech involvement in this project has been very minimal lately, as Scimedx, the manufacturer of retinol binding protein enzyme immunoassay (RBP-EIA), continues to prepare for marketing the product.. Commercialization activities to expand the market are expected to recommence in the third quarter of 2008, in collaboration with Scimedx,

Achievements and progress in the past six months

- None.

Problems encountered and actions taken to resolve them

- None.

Next steps and milestones expected in the next six months

- Initiate work with Scimedx to identify factors that could facilitate the scale-up of the use of RBP EIA.

Innovative micronutrient diagnostic tests

Goals of project

The goal of the Micronutrient (MN) Diagnostics Task Force is to identify candidates for a rapid, reliable, and easy-to-use screening tool for assessing micronutrients and indicators of infection/inflammation from fresh capillary blood or blood dried onto filter paper. To this end, the project has five main activities.

- Activity 1: Assess feasibility of developing rapid MN diagnostic tools.
- Activity 2: Conduct stakeholder meetings to gain consensus on public health need and uptake.
- Activity 3: Conduct market research to explore commercialization potential for downstream markets.
- Activity 4: Develop a product development plan.
- Activity 5: Develop laboratory proof of concept on one or two of the proposed tools.

Status of project as of March 2008

As part of the feasibility assessment to identify potential platforms for population-based and point-of-care tests, a comprehensive literature review was completed that reviewed over 100 publications for existing analytes and available commercial tests for vitamin A (retinol and retinol binding protein (RBP), iron deficiency (serum ferritin, serum transferrin receptor, transferrin, serum iron, zinc protoporphyrin), zinc deficiency (serum zinc), iodine, markers of inflammation (c-reactive protein and alpha-1 glycoprotein) and certain infections such as malaria. We are deciding whether to develop a surveillance test that could either provide population estimates of MN deficiencies or a point of care test that estimates the proportion of anemia attributable to iron deficiency or malaria. The review was partly focused on documenting the existing analytes and available commercial tests for a tool to screen for hemoglobin (Hb), ferritin, transferrin receptor, and c-reactive protein (CRP). The review identified three commercial manufacturers (Hemocue[®], iStat[®], and Spotchem IM) for exploring possible development activities for the anemia etiology test. For a multiplexed surveillance tool of Vitamin A, iron, and zinc deficiencies the review focused on potential platforms rather than specific commercial tests in use.

To identify user preferences for the types of platforms and priority micronutrients, a needs assessment survey was posted on a SurveyMonkey website and invitations were sent to over 350 participants to respond. Over 60 individuals have responded to date, and the survey is being sent to clinicians to obtain input on the perceived usefulness of micronutrient point-of-care tests for the treatment of infectious diseases.

Achievements and progress in the past six months

- A needs assessment survey for nutritionists was completed and analyzed.
- A narrowed list of diagnostic tools, focusing on surveillance and point-of-care assessment methods for measuring micronutrients was drafted.
- Private-sector entities were contacted for potential collaboration.
- Alternative funding was identified for exploring the technical feasibility of some of these tools, beyond the HealthTech work.

Problems encountered and actions taken to resolve them

- Responses to the survey came from the nutritionist community and not clinicians who manage anemic and iron-deficient patients. In order to get more balanced feedback, direct one-on-one interviews were conducted over the phone with a select group of clinicians from malaria- and helminth-endemic areas in sub-Saharan Africa.

Next steps and milestones expected in the next six months

- A tool will be selected; and specific indicators identified.
- PATH summary document of the literature review will be completed.

- User needs survey will be completed and report available.
- Industry landscape on selected technologies will be completed.

Low-cost methods for determining the bacteriological quality of drinking water

Goals of project

The goal of this project is to investigate the feasibility of creating simple, affordable, and effective field tests as indicators of fecal contamination in water of developing-world countries. In partnership with the University of North Carolina (UNC), we are examining available tools to measure fecal coliforms in drinking water in the absence of conventional laboratory facilities and skilled personnel, with special emphasis on (1) incubation at various possible ambient temperatures, and (2) the usability of low-cost culturing containers.

Status of project as of March 2008

The work on this project has been completed and we are awaiting responses to the publication submission (see below).

Achievements and progress in the past six months

- Completed culturing and performed testing on five platforms, including membrane filtration with culture on two separate media—MPN testing and the Petrifilm system. A final report on PATH activities was written and submitted to USAID. The finding concluded that it is possible to culture *E. coli* at temperatures from 22°C to 40°C. However, 45°C gave inconsistent results strain to strain. This would allow testing using some standard methods without use of an incubator to test for fecal contamination of drinking water supplies.
- An abstract was submitted to the American Society of Microbiology (ASM) for the general meeting in June 2008, and accepted for presentation as a poster. The poster is being produced as of April 2008.
- A paper was written and submitted to *Applied Environmental Microbiology*, and is in review as of April 2008.

Problems encountered and actions taken to resolve them

Despite our efforts and requests, we have received no final report from Mark Sobsey, Professor of Environmental Microbiology, and therefore we can not include his work in this report. We have acknowledged his contributions to the project (*E. coli* strains received and initial concepts used) in our publication submissions.

Next steps and milestones expected in the next six months

- The poster will be presented at ASM on June 2, 2008.
- Results are pending on the peer-reviewed paper. The reviewers' comments will determine response in terms of edits and/or possible submission to a different journal, if necessary.

Intradermal vs. intramuscular delivery of influenza vaccine in immunocompetent elders

Goals of project

Intradermal (ID) administration of influenza vaccine shows promise as an alternative to intramuscular (IM) injection, the current standard of care. Intradermal injection may more reliably deliver antigens to immune cells as the skin contains large numbers of dendritic cells which are the most potent antigen-presenting cells for eliciting primary immune response. Dendritic cells in the skin may be involved in both humoral and cellular responses.

Prior studies of influenza vaccine delivered intradermally have not compared equivalent doses of vaccine administered by different routes and have not focused on the elderly. We hypothesize that in older individuals a reduced dose of influenza vaccine given by the ID route may achieve the same degree of protection. We also believe that an equivalent dose given by the ID route may achieve greater protection as determined by the standard measure of immunogenicity, the serum hemagglutination inhibition (HAI) antibody titer one month following vaccination, as well as by an evaluation of the cellular (CD4+ and CD8+ T cells) response pre- and post-vaccination.

Status of project as of March 2008

HealthTech conducted a study with funding provided from the National Vaccine Program at the Centers for Disease Control (CDC) through USAID. Working with the Veterans Affairs Puget Sound Healthcare System (VAPSHS) and Vanderbilt University, the project team conducted a Phase 2 randomized controlled trial to assess the safety and immunogenicity of ID delivery of a licensed inactivated trivalent influenza vaccine of varying dosages in immunocompetent elders age 65 and over. The safety and immunogenicity of ID injection was compared to IM delivery of influenza vaccine. In addition, the cellular immune response of ID injection to IM delivery will be evaluated in a subset of 30 individuals.

This study addresses a crucial area of investigation both to improve annual influenza prevention and to prepare for pandemic influenza. In times of vaccine shortage, whether in interpandemic or pandemic periods, knowing if reduced doses of influenza vaccine can be given intradermally with the same immunologic effect as higher doses of vaccine given in the usual manner will allow health care providers to maximize the available influenza vaccine. Furthermore, improved vaccine effectiveness may decrease adverse health consequences of influenza in the elderly population. The study commenced on September 5, 2007, and vaccinations continued through October 26, 2007.

Achievements and progress in the past six months

- The study successfully enrolled a total of 259 participants.
- The blood samples for the humoral response were tested and analyzed.
- Study results were presented at The Mérioux Foundation's conference on intradermal delivery of vaccines held in Annecy, France, from April 7–9, 2008 and concluded the following:
 - Local reactions of redness, swelling, and itching were significantly more frequent among recipients of ID injections. ID vaccination was otherwise well-tolerated, with pain and systemic symptoms comparable to IM injections.
 - Influenza vaccine at 60% dose by either IM or ID route achieved comparable antibody titer, and were similar to full dose IM vaccination among highly vaccinated, healthy elderly.
 - There was no difference in priming by ID and IM routes. Subsequent full dose vaccination after reduced dose vaccination by either route did not increase seroprotection rate.

Problems encountered and actions taken to resolve them

- The study was selected for an audit by the United States Food and Drug Administration (USFDA). The audit occurred the week of February 26, 2008, with minor issues related to the study conduct,

monitoring, and reporting. The findings fell into the category of “voluntary action,” and the site will prepare a written response to the FDA to address the issues reported in the audit.

- We originally expected to enroll 300 participants but were successful in enrolling only 259. Late recruitment occurred due to a delay in the agreement being signed between PATH and the Seattle Institute for Biomedical and Clinical Research (SIBCR), as well as the influenza vaccine not being available to this population as early as expected. By the time our study was set to begin recruitment and enrollment, many eligible seniors had already received their vaccinations elsewhere. Therefore, we made the decision not to enroll patients past October 26 due to the possibility of a vaccination having already been received and/or the flu season already begun, thus increasing the possibility of real infection confounding the data. In looking at the numbers, the Principal Investigator (PI) and co-PI felt very strongly that stopping around 240 would still give us the information we needed without compromising the data.

Next steps and milestones expected in the next six months

- Presentation of the study results at the American Geriatric Society’s annual meeting to be held May 2, 2008, in Washington, DC.
- Full results (both HAI and T-cell response) will be analyzed.
- The study results will be compiled into a manuscript and submitted to an appropriate journal for publication.
- The study will be closed with the Western Institutional Review Board and the University of Washington’s Institutional Review Board.

Rapid human papillomavirus (HPV) antibody test

Goals of project

The goal of this project is to determine the feasibility of a rapid, non-instrumented, near-patient immunochromatographic strip (ICS) test for antibodies generated against high-risk HPV types 16 and 18 in a plasma-based sample. Demonstrated feasibility of such a prototype device could lead to development of rapid tests utilizing noninvasive samples (e.g., oral fluid) potentially suitable for treatment and/or vaccine modalities.

Status of project as of March 2008

Funding for the project was provided to HealthTech via USAID from the National Vaccine Program under last year's Unmet Needs program, so the rapid HPV antibody ICS test is still in the formative research stage. We are currently working with collaborators to secure the reagents necessary to perform the laboratory research. Research plans have been prepared and work is ready to begin when the reagents arrive.

Achievements and progress in the past six months

- Project received initial funding and has begun.
- We are working with collaborators to identify and secure reagents.
- HealthTech has assessed the field for other suitable, commercially available reagents.
- We have prepared research plans and have begun to identify product specifications.

Problems encountered and actions taken to resolve them

- Slow response from collaborators providing critical reagents has hampered the ability to perform laboratory-based research. The interim time has been spent identifying alternate sources of critical reagents and planning experiments for when the reagents are received.

Next steps and milestones expected in the next six months

- HealthTech will proceed with the technical research once the reagents are identified.
- We will consult literature and consultants on the importance of detecting each immunoglobulin class and determine if differentiation is important.
- We plan to assess detection technologies for optimal detection of IgG and evaluate detection technology for cross-reactivity with other immunoglobulin classes.
- We will evaluate systems with available immunoglobulin classes (targeting HPV, if available).
- We will assess rapid assay platforms suitable to achieve project goals; and assess multiple solid- and mobile-phase options available for the best platform.
- Once a prototype is available we will evaluate prototype assay with negative samples spiked with purified HPV antibodies, as well as with panels of characterized blood-based samples from clients infected (or previously infected) with HPV.
- We will also decide the best detection strategy for the test and the best assay format including materials, solid-phase and mobile-phase chemistries, and assay reagents.
- Finally, the prototype assay will be evaluated with spiked and blood-based samples.

Element: HIV/AIDS

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; most importantly, it will empower clinicians and patients to control the expanding epidemic.

Status of project as of March 2008

Presently we are collating and summarizing data from the past year of experimental work working with our collaborator – PortaScience - in an effort to create a strategic plan for moving the technology forward aggressively in the coming months. To date, we have shown repeatedly that the detection system is adequate for the task required at hand. The purification system, necessary to give specificity in detection, requires further optimization.

Achievements and progress in the past six months

- PATH, in collaboration with PortaScience Inc. has determined a new lower limit for the threshold of detection with the Porta WBC strips (5 cells/ μ l). This is well within the range desired to provide accurate semiquantitative results for important CD4 count categories, particularly in the lower end of the range.

Problems encountered and actions taken to resolve them

- Our recent attempts to develop a simple, room temperature, and inexpensive CD4 cell purification system have been unsuccessful to date. We have demonstrated that a smart polymer-based magnetic nanoparticle system can capture greater than 95 percent of cells in a whole blood matrix. However, this system does not provide specificity in its capture and consequently captures other leukocytes that react with the Porta WBC membrane.
- We are conducting a repeat scan of the literature and commercial landscape in an effort to identify new methods for developing a simple purification module. Our goal is to design and implement sets of experiments with at least two new methods in the coming months.
- The funding provided by USAID is essentially gone, so we will need to identify other funding to continue this project. We had support for awhile from the CD4 Initiative funded by the Bill and Melinda Gates Foundation, but that support also ended in September 2007.

Next steps and milestones expected in the next six months

- If adequate funding is secured, we will focus all of our efforts on developing a simple purification module that can be adapted for use with the Porta WBC membrane-based detection system.

Microbicide applicator project

Goals of project

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

Status of project as of March 2008

We have advanced the development of several new microbicide delivery methods over the last six months, including an improved “dose-limiting” paper applicator, a “dose-metered” vaginal applicator, and the SILCS Diaphragm for controlled microbicide release. Each of these delivery options could offer benefits to different populations, and we expect to advance the paper applicator into clinical trials this year to evaluate its usability and safety with a chosen microbicide.

Achievements and progress in the past six months

- HealthTech received refined dose-limiting paper applicators that represent a second round of design modifications by the manufacturer, Tekpak. HealthTech has conducted initial bench tests with these devices to assess filling and dispensing; results indicate that these devices are superior to the last batch received and address some key usability concerns. We are in the process of collecting documentation on the product materials to be able to include in future clinical study submissions.
- HealthTech identified a German manufacturer that specializes in paper devices (including applicators), and which has supplied paper applicators to pharmaceutical companies, such as Janssen-Cilag, that markets its products in South Africa and elsewhere. We have contacted them to collect samples and cost information that will allow us to compare their products with the US-based manufacturer, Tekpak. This is an important step that will enable us to avoid single-source supplier issues and will allow us to advance the most cost-effective, appropriate device into clinical trials.
- HealthTech established a collaboration with a South African design firm, LTN, to develop a user-filled dose-metered vaginal applicator. They have provided numerous design concepts based on our design specifications and have succeeded in designing a simple mechanism that will ensure accurate and complete filling and dose delivery.
- HealthTech’s collaboration with Queens University of Belfast has resulted in additional data supporting proof-of-concept of a controlled-release SILCS Diaphragm.
- Studies conducted over the last six months include:
 - Evaluation of a modified SILCS model has demonstrated increased reproducibility in a 14-day release study of dapivirine compared to the original SILCS model developed for *in vitro* testing.
 - Mechanical testing of numerous polymeric materials was conducted to compare against the mechanical properties of the SILCS spring (nylon-6) to identify best materials for further *in vitro* testing.
 - Conducted a 14-day release study using new polymeric materials and the improved SILCS model to assess intra-day release profiles (e.g., release of dapivirine over first 8 hours compared to 14-day overall release rate profiles). Intra-day release rates are consistent with expected results given daily release profiles of same materials.
 - Conducted a 4-week discontinuous use study to measure release rates when the SILCS model is placed on release for 8, 12, and 24 hours, followed by 1 week of no use, then put on release for same time points and repeated for 4 weeks. Results illustrate that release rates pick up at the same place they dropped off the prior week. Findings were consistent with expected release profiles. This study and the intra-day release study were conducted to better model possible diaphragm use regimens.
 - Conducted an *in vitro*, 14-day release study with the modified SILCS model to evaluate the change of release rates based on an increased diameter and a decreased thickness of silicone tubing. Release rates of dapivirine increased as expected for changes in key release variables.

- HealthTech has established a three-way collaboration among PATH, Queens, and CONRAD for use of UC781 in future product development work on SILCS as a controlled-release microbicide delivery device. Midterm assessment (MTA) has been reviewed by all parties and is expected to be in place by the end of the month.
- Results of the acceptability and dose delivery study were presented in poster format at the Microbicides 2008 Conference in India.

Problems encountered and actions taken to resolve them

- We have encountered a delay in the initiation of our proposed Phase 1 clinical trial of the paper applicator with a microbicide. This is due to two reasons: (1) additional development was needed to improve the modified paper applicator with a dose-limiting stop, and (2) we have not identified a microbicide sponsor who wants their product to be used for this trial. To address the applicator design problems, we provided technical guidance and financial support to Tekpak to make the necessary design improvements. Regarding selection of a microbicide, we have had initial talks with CONRAD regarding use of UC781 and Indevus regarding use of Pro2000. While both have expressed interest in having their gel used in the study, both identified the timing of this study (i.e., 2008) as problematic. In mentioning this issue to USAID, during the Microbicides 2008 Conference in India, it was suggested a teleconference be held with a broader group of people to strategize about the best method for moving forward. We will schedule this for the next month pending availability of key participants.

Next steps and milestones expected in the next six months

- In the next six months, HealthTech will receive samples of paper applicators and cost information from German manufacturer; conduct bench testing and in-house user evaluation to compare product to Tekpak applicator. We will determine whether German device should advance into clinical trials (i.e., evaluate trade-offs in cost, usability, dosing, accessibility).
- We plan to evaluate two rounds of rapid prototypes of dose-metered applicator made by South African design firm, and will advance the design that best addresses HealthTech design specifications. The final deliverables due in January 2009 will result in functioning prototypes from manufacturing grade materials that have been validated for performance and dose delivery.
- In collaboration with Queens University of Belfast, we will continue evaluating the feasibility of the SILCS as a controlled-release delivery device—including development of new *in vitro* models that more closely model the SILCS device and diaphragm use-regimens. Initiate use of UC781 for *in vitro* testing and explore access to additional model microbicides, such as dapivirine (through direct access from Johnson & Johnson [J&J] instead of through the International Partnership for Microbicides [IPM]) and possibly newer candidates currently being evaluated by the National Institutes of Health (NIH).
- We plan to confirm interest and establish a collaboration with a microbicide sponsor for incorporation of their microbicide in the Phase 1 study of the paper applicator with a microbicide.

SILCS microbicide delivery system: couples' acceptability of alternate gel scenarios

Goals of project

This pilot study will explore the feasibility and acceptability of the SILCS microbicide delivery system (MDS) when used by couples who evaluate two gel dosing scenarios and compare these to gel delivered by a vaginal applicator over multiple uses. The outcome of this project is two fold: to identify women's preferred scenario for gell application, and to provide preliminary assessment of how gel volume and gel application scenarios influence acceptability for the woman and her partner across a range of measures.

HealthTech funds have also supported PATH's work with donors, researchers, and other stakeholders to position the SILCS as a MDS and to monitor the pivotal study being conducted by CONRAD.

Status of project as of March 2008

Project activities began in late Fall 2007 following the initiation of a preliminary feasibility study to test the gel scenarios being considered for this use acceptability of the SILCS-MDS among couples, using separate funding. In December, we negotiated a subagreement with the California Family Health Council (CFHC) to collaborate on planning and implementation of this study. The study outline has been drafted and reviewed. Final work on the study protocol is pending selection of the microbicide product to include in this study, and while we await results from the feasibility evaluation in Seattle of the gel application scenarios.

Achievements and progress in the past six months

- Using other funding, PATH initiated a background study of gel scenarios in Seattle to test the feasibility and ease of handling (during gel loading, insertion, wear, and removal) of the gel scenarios being considered for the CFHC study.
- Under HealthTech???? a subagreement with CFHC has been negotiated and signed by both parties.
- HealthTech and CFHC drafted the preliminary outline of the study procedures.
- Meanwhile, HealthTech staff met with stakeholders to assess the rationale and potential advantages or challenges of several microbicides being considered for this study. The stakeholders confirmed that incorporating BufferGel into this study would be advantageous.
- Acceptability measures of the SILCS-MDS and gel application scenarios are under development.
- Instructions for the various gel scenarios have been drafted and reviewed and are being revised.
- HealthTech staff met with donors, diaphragm researchers, and microbicide sponsors at the Microbicide 2008 Conference in February to begin clarifying the research agenda for diaphragms in a post-MIRA (Methods for Improving Reproductive Health in Africa) environment.
- In a related activity with separate funding, PATH was invited to facilitate an on-line discussion about diaphragms hosted by the Implementing Best Practices (IBP) community as part of their effort to publicize the document, Family Planning: A Handbook for Providers. This discussion will provide an opportunity to raise questions to a broader community about the potential role of diaphragms for dual protection.

Problems encountered and actions taken to resolve them

- Development of the protocol was delayed while we investigated the advantages of various microbicides before deciding which gel to include in this study. The stakeholder consensus confirmed interest in using BufferGel in this study. Conversations with ReProtect were initiated in April, and a verbal agreement to use BufferGel in this study has been reached.
- Now that HealthTech has decided to use BufferGel as the microbicide in this study, some of the study procedure questions around gel volume are resolved, since BufferGel is delivered as a 5-ml dose.

HealthTech staff and ReProtect are discussing how to split the dose for the gel scenario when gel is applied to both the vaginal and cervical sides of the diaphragm.

- Until results of a preliminary feasibility study that is assessing the gel scenarios being considered for the CFHC study are available, we cannot finalize the procedures and instructions for applying the gel to the cervical side and the vaginal sides of the diaphragm. Recruitment for this study has been slower than expected; results from the feasibility study are expected in May.

Next steps and milestones expected in the next six months

- PATH and ReProtect will sign a materials transfer agreement for use of BufferGel use in the study and study procedures for gel application confirmed.
- Acceptability questionnaires and all relevant study documents completed.
- The protocol will be finalized and submitted for review and approval by relevant institutional review boards and CFHC will begin recruitment/enrollment.
- HealthTech continues to participate in discussions to shape the research agenda for diaphragms.
- HealthTech facilitates the on-line IBP diaphragm discussion, tentatively scheduled for June (with separate funding).

SILCS microbicide delivery system assessed through MRI

Goals of project

The goal of this proof-of-concept pilot study is to assess the feasibility of the SILCS Diaphragm to deliver microbicide gel to the cervix and vaginal canal when assessed by magnetic resonance imaging (MRI) and compared to the dispersion and retention when gel is delivered by a standard vaginal applicator. The candidate microbicide BufferGel[®] (manufactured by ReProtect) will be used as the gel in this study.*

Status of project as of March 2008

PATH initiated this project in November 2007. Subagreements with both the University of Pennsylvania and Brown University/Lifespan have been signed and a protocol planning meeting was held in December 2007. Protocol development is nearly complete. An acceptability framework that incorporates both device and microbicide acceptability measures has been drafted and is being reviewed. An agreement with ReProtect has been drafted to cover the transfer of materials for this study. We anticipate the study protocol will be ready for institutional review board (IRB) review by May 2008. The clinical portion of this study is expected to be underway by the end of June 2008.

Achievements and progress in the past six months

- The HealthTech team, with Kate Morrow from Brown University/Lifespan, developed a draft framework for assessing user's experience with the SILCS microbicide delivery system compared to a standard applicator. This is currently being reviewed. We plan to pretest the questions in May 2008.
- Kurt Barnhart's research group at the University of Pennsylvania with the HealthTech team drafted the study protocol. This is being reviewed by the three research groups in preparation for IRB review.
- Instructions for the three different gel delivery modes with SILCs are being revised and adapted for this study. These will be submitted along with the protocol and related study documents to the IRBs.
- PATH drafted a materials transfer agreement (MTA) to allow transfer of BufferGel from ReProtect to the University of Pennsylvania. This document is under review by the parties.
- We also submitted a request to the USAID Microbicides Account for FY2008 funding to support year-2 activities related to bringing the study to completion.
- The core scope of work for this study included three MRIs for each of the women who will be enrolled. At the December 2007 meeting, the investigators agreed it would be valuable to include a final MRI scan after each woman has worn the SILCS Diaphragm for six hours. This final scan will allow a more complete data set and help answer whether delivering gel with the SILCS Diaphragm improves gel retention when compared to gel delivered by a vaginal applicator. (Since current clinical guidelines recommend women wear the diaphragm six hours after intercourse, the final MRI will capture the state of the gel across all three gel delivery modes at the point where women are advised to remove the diaphragm.) PATH has obtained funding from another source to support this fourth MRI and the costs associated with interpreting the scans. This expanded scope has been incorporated into the study protocol.

Problems encountered and actions taken to resolve them

- Start of the project was delayed until mid-fall 2007 while we waited to learn whether the National Institutes of Health (NIH) would support this study through the Microbicide Innovation Program (MIP II). Once the NIH confirmed this study was not included in their portfolio, we adapted the study outline and began to move forward with HealthTech funding.

Next steps and milestones expected in the next six months

- Plans will be finalized with the University of Pennsylvania Industrial Research Pharmacy for mixing the gadolinium into the BufferGel and filling the mixed gel into dose applicators for the study.
- The acceptability framework will be finalized, pilot tested, and prepared for IRB submission.

- The study protocol will be submitted to the University of Pennsylvania IRB and the PATH Human Subjects Protection Committee for review.
- Upon IRB approval, participants will be screened and enrolled and MRI scans will be completed for the first gel application mode.
- USAID will notify PATH if year-2 funds are approved to cover costs for the second year of this study.

*BufferGel[®] is the same microbicide being evaluated with the SILCS device in the pivotal contraceptive effectiveness study.

Element: Other

Liquid culture diagnostic for tuberculosis and drug susceptibility testing

Goal of project

The goal of this project, using limited funds still available from the USAID tuberculosis earmark funds, is to develop an accurate and simple test for determining multi-drug resistant tuberculosis (MDRTB) using the microscopically observed drug susceptibility (MODS) approach that is affordable and useful for populations in the developing world.

Status of project as of March 2008

- The project has progressed rapidly in the past six months.
- We have signed a collaboration agreement with the Tulip Group of Companies (Goa, India) to manufacture the MODS kits. They are currently creating a first-generation prototype for a collaborative evaluation in India and possibly Peru.

Achievements and progress in the past six months

- PATH signed a collaboration agreement with Tulip Group of Companies.
- HealthTech staff met with Tulip and collaborators from Imperial College (inventors of the MODS approach, based in Peru) in Goa to define product specifications and plan laboratory and field evaluations.
- Staff also met with collaborators at the Lepra Society (Hyderabad, India) who have agreed in principle to serve as a laboratory evaluation site for the first-generation MODS kit prototype.
- We also met investigators at other possible laboratory and clinical evaluation sites for the MODS kit prototype. These included the TB Research Center in Chennai and the Christian Medical College in Vellore.

Problems encountered and actions take to resolve them

- HealthTech did not receive additional funding from USAID to continue this project.
- We applied to the Schwab Foundation and to internal PATH sources of funding to keep the project moving forward. We did not get the Schwab award, but have acquired internal funding to support these efforts for now.

Next steps and milestones expected in the next six months

- First-generation MODS kit prototype will be completed by our commercial partner.
- Preliminary laboratory-based evaluation of this kit will be initiated.
- The clinical site for evaluation of the MODS kit will be selected.
- The protocol for the clinical evaluation of this kit will be started.

Skunkworks

Sample processing for RNA stabilization and emerging point-of-care molecular diagnostics

RNA is the target biomarker of choice for several pathogens of significant global health impact, including viral influenza, HIV, dengue, hepatitis C, and measles. RNA is also unstable, and clinical specimens need to be preserved under cold chain until processed for testing. This is a major technical and cost hurdle for implementing surveillance and therapy diagnostics for RNA viral pathogens in low-resource settings. The overall aim of this project is to develop a low-cost, easy-to-use device that extracts and stabilizes viral RNA biomarkers in clinical specimens collected at remote clinical settings. This device should remove the need for the cold chain and also be useful for emerging point-of-care nucleic acid-based diagnostic tests. In the previous report we stated that we have demonstrated the proof of principle for such a device.

With this most recent skunkworks funding under HealthTech, PATH has focused on prototype design and development. PATH is developing a product to enable HIV-1 viral load testing in low-resource settings. With these funds specifically, (1) we have developed a product specifications document for the device as applied specifically to HIV-1 viral load testing; (2) we have initiated communications with the private sector to co-develop this device; (3) we are in the process of developing a user requirements questionnaire specifically around HIV-1 viral load testing to further inform the product development; (4) we have developed two alternate methods for RNA stabilization at the point-of-care without the requirement for cold chain; and (5) we have initiated designs for an integrated point-of-care RNA extraction and stabilization product.

Infant HIV proviral DNA capture card

Infant HIV diagnosis by standard immunoassay methods is complicated by the persistence of maternal antibodies in infants younger than 12 to 18 months. Assays employing nucleic acid amplification and detection of the virus are sensitive and specific for HIV diagnosis shortly after birth but utilize costly reagents and instrumentation, are technically difficult to perform, and require special storage and transport conditions. For polymerase chain reaction (PCR) testing, the current gold standard for remote sample collection and transport is filter paper blood spots (FPBS). Current filter paper-based collection efforts are limited by the high concentration of PCR inhibitors (e.g., red blood cells [RBC] on the membrane surface). Subsequently, only a small fraction of a specimen can be used in the assay or complex, expensive methods are employed to remove inhibitors.

HealthTech proposes to develop a membrane system that simultaneously enriches proviral DNA by capturing it on the membrane surface and eliminates common PCR inhibitors by allowing them to flow through to a wicking pad below the membrane. This method is compatible with the current practice of collecting blood on filter paper and would require little additional training but would dramatically improve assay sensitivity as well as eliminate a number of downstream processing steps. Furthermore, the components of this membrane system are available commodities and would not add substantial cost to the assay.

We are currently developing a two-component membrane system that uses capillary action to wick RBC away from peripheral blood mononuclear cells (PBMC). HIV-1 proviral DNA is integrated into the genomes of PBMC. Thus, by capturing PBMCs and their DNA, one captures HIV-1 proviral DNA. We have evaluated a variety of membrane systems and capillary mechanisms for removal of RBC from PBMC samples. Two membrane systems have been shown to be promising candidates for further development of our proposed sample collection and enrichment device. Between October 2007 and March 2008 we collected the relevant background information on the source and quality of MMM5 and Leukosorb membranes. We contracted PortaScience to manufacture 300 proviral DNA capture cards (PDCCs) of each membrane for preliminary PCR experiments. We also needed a non-HIV one copy gene target for validation of the card before moving into HIV infected PBMCs. We identified the gene target

glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and designed and ordered primer and probe sets for real time PCR assay. The first phase GAPDH experiments were designed and a consultant hired to perform the assay. Relevant literature was also collected on current PCR assays used in programmatic settings in sub-Saharan African countries and on algorithms recommended by WHO and pediatric HIV international organizations.

Immunochromatographic strip readers

Many point-of-care strip tests suffer from poor sensitivity or sensitivity that is not adequate to make the test clinically useful. With HealthTech and other funding, PATH is developing a fluorescent detection system for strip tests that we hope will improve sensitivity of tests. To date, we have developed a europium latex conjugate that can be excited using a simple ultraviolet light source and emits in the visible spectrum. We also are developing a simple, handheld reader for this fluorescent approach that combines inexpensive CCD camera optics, UV LED light sources, and data storage and analysis functionality found in many USB drives. Using a model system to detect *Chlamydia trachomatis*, we have improved the sensitivity of the strip test 160 times over the level of detection we observed with a standard colloidal gold system. Next steps include further optimization of the reader and fluorescent chemistries and retrospective and prospective evaluation of the system with clinical specimens.

Other Skunkworks Projects

HealthTech leadership has recently allocated more of the skunkworks funds to several inhouse projects that focus on innovative, new ideas for technology solutions. Since this assignment was done fairly recently, we will defer a report on any progress until the next semiannual report. Included on the list are the following:

- Enhancement of the immunochromatographic strip tests using nucleic acid amplification.
- Enhancement of the immunochromatographic strip test using a europium technique.
- Rapid low-cost herpes simplex virus 2 test.
- Preeclampsia screening tool.
- Radio frequency identification device for use in the cold chain
- Auto-reconstitution syringe.
- Microneedles for vaccine delivery.

Mfrp24913

File code: 520.01.03.J