

HealthTech IV

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Highlights and milestones of HealthTech projects during the past six months

- Developed a preliminary global roll out timeline for depo-subQ provera 104™ injectable contraceptive in the Uniject® prefilled injection device. The timeline is being discussed with USAID, Family Health International, and John Snow Inc.
- Updated the SILCS Diaphragm production and design engineering drawings and developed a cost of goods model. These are steps in our effort to build manufacturing and commercialization partnerships worldwide for the introduction of the device in key countries.
- Developed comprehensive clinician-specific and consumer-specific discussion guides and a product profile of the SILCS device to test attitudes, assumptions, and potential interest. These documents will be used in primary research interviews with reproductive health providers and potential users in the United States, Canada, and Western Europe (United Kingdom, Germany, and France) as well as China, India, and Brazil.
- Conducted user needs assessments in Kenya and Zambia to inform development of specifications for an affordable point-of-collection device that will classify individuals' anemic status and elucidate the potential causes of anemia. The information gathered in these assessments has been used to write product specifications that meet the needs of multiple markets.
- An operations research study in Sylhet, Bangladesh, that included chlorhexidine for umbilical cord care produced by Popular Pharmaceuticals Ltd. was completed. HealthTech staff participated in the results dissemination workshop organized by the Projahnmo group in Dhaka at the end of September 2009.
- Traveled to Nepal to conduct final data collection activities for a field evaluation of gentamicin in the Uniject® prefilled injection device. The field evaluation is now complete and preliminary data analysis suggests that using gentamicin in the Uniject® prefilled injection device as part of community-based management of neonatal sepsis is feasible and acceptable to health workers and the community.
- Conducted T-cell assays following the completion of a Phase 2 randomized controlled trial to assess the safety and immunogenicity of intradermal delivery of a licensed inactivated trivalent influenza vaccine of varying dosages in immunocompetent elders age 65 years and over. T-cell response revealed low interferon-gamma and tumor necrosis factor-alpha expression by CD4 or CD8 cells following intradermal and intramuscular vaccination.
- Completed the final report from the situational analysis of neonatal resuscitators for essential newborn care in selected states in India in collaboration with the government of India, USAID/India, World Health Organization-India office, United Nations Children's Fund, IndiaCLEN, and PATH's office in India. The report was printed and distributed to key stakeholders in India.
- Provided technical assistance to Instituto Biologico Argentino (BIOL) to prepare for the World Health Organization (WHO) prequalification process. BIOL submitted a dossier to WHO in June of 2009 for prequalification of both oxytocin in the Uniject® prefilled injection device and ampoule (10 IU) presentations.
- BIOL registered its oxytocin in the Uniject® prefilled injection device product in Guatemala and officially launched commercial sales in Argentina.
- Drafted a use-case catalog that outlined the system behavioral requirements. To achieve this end the team detailed scenario-driven threads through the functional requirements for Cold Chain Equipment Manager (CCEM) software. A software development firm has been hired to complete the necessary design, coding, testing, and user interface improvements and will deliver a validated version of the CCEM software tool. This version of the tool, version 2.1, developed in Microsoft Access 2007, will include improved usability and graphic design.
- Completed a phase change material (PCM) landscape for the Twinbird Stirling cooler vaccine refrigerator. Various design analyses and experiments have been conducted with regard to meeting

Performance, Quality, and Safety (PQS) holdover time. Two PCM liner configurations were developed that meet the PQS holdover time—both designs require no manufacturing change to the current Twinbird product.

- Drafted and submitted to WHO the PQS language enabling inclusion of the battery autonomy calculation tool as a normative reference for solar-powered vaccine refrigerators. The battery autonomy design tool was developed by HealthTech and is based on long-term measured solar radiation data that enables refrigerator developers and manufacturers to design products to fit real world needs in which vaccine refrigerators must store energy for nights and days with cloudier weather. We have added data for all tropical locations included in the World Radiation Data Centre database with at least a five-year record of ground-based measurements. These data accompany the battery autonomy calculation tool.
- Collaborated with the Making Medical Injections Safer project in the identification of African manufacturers of high-quality safety boxes for sharps waste that could meet WHO PQS standards. Safety boxes from two Kenyan and one Ethiopian supplier were tested by a materials consultant at the University of Washington using paper board testing procedures to translate WHO's performance specifications (i.e., water resistance, puncture proof) into paper technical specifications (i.e., burst strength, density, and grammage). These technical specifications were shared with the Kenyan and Ethiopian manufacturers along with contact information for companies who sell high-grade paper board.
- Organized a meeting of the Strategic Advisory Group formed at the Symposium on Advancing Prevention Technologies for Sexual and Reproductive Health where working groups reported results from mapping exercises describing status of current and future multipurpose prevention technologies. HealthTech chaired one of the working groups and worked with group members to articulate the mission of this sexual and reproductive health initiative. The group brainstormed short- and long-term priorities for inclusion in a funding case.
- Participated in the WHO/Joint United Nations Programme on HIV/AIDS's technical consultation on Preparing for Access to PRO 2000 and incorporated microbicide applicator bridging studies into the priority activity list.
- Initiated focus group discussions to familiarize researchers and the Shanghai reproductive health community with the Woman's Condom device. Data collection is currently underway with nine potential user segments.

Element: Family Planning and Reproductive Health

Exploring cost reduction of levonorgestrel-releasing IUD

Goal of project

This project is exploring strategies and opportunities for expanding access to a levonorgestrel-releasing intrauterine device (LNG-IUD). The project is investigating opportunities for expanded access to the existing product, as well as characterizing efforts underway to develop and bring to market a lower-cost version of a hormonal IUD. This project fits within the goal of expanding access to underutilized reproductive health technologies.

Status of project as of September 2009

Through informal contacts and desk research, HealthTech continues to investigate initiatives to bring to market a lower-cost LNG-IUD. During the past six months, we met with and reviewed a proposal by the US-based nongovernmental agency, Venture Strategies, to produce and commercialize a lower-cost version of the LNG-IUD. Their proposal was not strong on commercialization details but they were seeking international regulatory assistance to guide approval of a combination product. HealthTech helped introduce them to contacts with an international regulatory group. We continue to monitor development initiatives in Europe and South America to assess the feasibility of these efforts to develop a generic LNG-IUD. We also are exploring contacts with steroid and IUD manufacturers in India and China to see if manufacturers from these regions are undertaking initiatives that could bring down the cost and improve access to a hormonal IUD.

We also are seeking to characterize the potential health impact of an LNG-IUD and where broader access to an LNG-IUD would have greatest health impact in order to strengthen the value proposition for this technology.

Informal feedback from Bayer Shering Pharma of Germany, the current manufacturer of LNG-IUD, continues to confirm there is no market rationale for them to voluntarily lower the cost of the LNG-IUD.

Achievements and progress in the past six months

- Briefed PATH staff at the Secretariat of the Reproductive Health Supplies Coalition (RHSC) about findings from this project to date.
- Enlisted assistance from Belgium-based John Skibiak, Director of RHSC, to follow-up with HRA Pharma, one of the European companies we have been monitoring regarding new developments.

Problems encountered and actions taken to resolve them

HealthTech staff previously reported on a privately-funded, US-based initiative focused on improving access to a lower-cost LNG-IUD for United States public-sector markets. Due to the economic downturn, however, recent reports show that this initiative has been delayed, and for public-sector international IUD programs as well. We are waiting for further reports on the status of this project. We remain in contact with this organization and are seeking information from external contacts to determine when this project might resume activity.

Next steps and milestones expected in the next six months

- Complete a review of product development initiatives underway; characterize the status of each initiative and identify obstacles to be addressed.
- Complete interviews with stakeholders to assess perspectives on the role of a therapeutic IUD within the context of public-sector IUD programs and to identify populations/countries where expanded access would be feasible.
- Summarize findings to USAID and other IUD stakeholders.

Introduction of depo-subQ provera 104™ injectable contraceptive in the Uniject® prefilled injection device

Goal of project

The goal of the project is to increase the safety, acceptance, and reach of injectable contraceptives through advancement and introduction of depo-subQ provera 104™¹ injectable contraceptive in the Uniject®² prefilled injection device for family planning programs. This product will facilitate innovative new options such as home injection of contraceptives and applications related to outreach.

Status of project as of September 2009

Pfizer is currently proceeding with a European Medicines Agency submission of depo-subQ provera 104 in the Uniject device for regulatory approval, with USAID priority country registration to follow. HeathTech is ramping up staffing and planning efforts for an expanded role in the development and implementation of the USAID work plan for global roll out of the product. This will include convening partner meetings, project management and coordination, communications planning and implementation, liaising with key implementation partners, and development of training materials for acceptability studies and eventual global rollout.

Achievements and progress in the past six months

- Presented at a Pfizer internal marketing planning meeting in April 2009.
- Developed a preliminary global roll out timeline for discussion at a meeting with USAID, Family Health International (FHI), and John Snow Inc. (JSI) in June 2009.
- Assisted Pfizer in holding a donor's meeting at Pfizer's New York headquarters in July 2009.
- Disseminated results of the rapid survey of field program interest to key stakeholders.
- Participated in a Technical Advisory Group meeting and other meetings facilitated by the Limited Introduction of depo-subQ provera 104 in the Uniject™ Device project, funded by the Bill & Melinda Gates Foundation. As part of this effort, HealthTech met with representatives from FHI, JSI, USAID, and the Gates depo-subQ provera 104 project to clarify work plan expectations and identify collaborative opportunities.

Problems encountered and actions taken to resolve them

Pfizer clarified that its registration and labeling of depo-subQ provera 104 in the Uniject device only indicates injection in the abdomen or thigh. As a result, injection in the arm as is currently practiced for the intramuscular formulation of Depo-Provera® will be considered by Pfizer as an off-label use for the subcutaneous product. The extent to which this will impact interest in the product or complicate product administration during acceptability studies and eventual product introduction is unclear.

PATH, USAID, and FHI have discussed this issue and identified the need for more in-depth review of the literature, the need to articulate a clear strategy for addressing these concerns, and the need to communicate with key stakeholders about it.

Next steps and milestones expected in the next six months

- Act as the key liaison between Pfizer; USAID; Becton, Dickinson and Co.; and others to ensure availability of product for pre-introductory studies and global rollout.

1. depo-subQ provera 104 is a trademark of Pfizer.
2. Uniject is a registered trademark of Becton, Dickinson and Co.
3. Depo-Provera is a registered trademark of Pfizer.

- Convene a meeting in December 2009 to bring together each of the key partners involved with the rollout and coordinate the implementation of work plan objectives.
- Prepare a comprehensive, multi-partner work plan for the USAID global rollout of depo-subQ provera 104 in the Uniject device.
- On behalf of USAID, lead the coordination of key partners to implement the work plan.
- Convene and facilitate rollout partner meetings and conference calls, as needed.
- In close coordination with FHI and USAID, lead the development and dissemination of training materials in support of planned acceptability studies in selected USAID-priority countries.
- Develop an overall communication plan aligned with the global rollout preparations over the next two years, including:
 - Clarification of the implementation partners, the information needs, and communication channels of key audiences such as USAID missions, USAID cooperating and bilateral agencies, and country ministries of health.
 - Participation in the development of informational materials for dissemination by USAID headquarters to appropriately engage and inform USAID missions in decision-making and early introduction planning. This may include adaptation of assessment tools and introduction planning work developed by the Gates depo-subQ provera 104 project.

SILCS Diaphragm commercialization

The next three HealthTech reports describe projects underway that lay the groundwork for commercialization of the SILCS Diaphragm once the product has been approved by the United States Food and Drug Administration. These projects will:

- Assess manufacturing and commercialization partnerships worldwide to plan for SILCS Diaphragm availability and affordability in key regions.
- Evaluate the commercial market for the SILCS Diaphragm, including distribution channels, to develop a strategic global access plan.
- Assess regulatory and commercialization implications of over-the-counter distribution in the United States and other markets.

Development of commercialization partnerships for the SILCS Diaphragm

Goal of project

The goal of this project is to develop commercialization partnerships to prepare for the introduction of the SILCS Diaphragm in key countries. With current funding, this first phase of activities focused on evaluating manufacturing options inside and outside the United States and developing a supply/demand forecasting model based on updated costs. This information will help ensure competitive supply of the SILCS Diaphragm for future introduction and will be used in negotiation with potential commercialization partners.

Status of project as of September 2009

HealthTech solicited proposals from production engineering firms for a manufacturing review. We reviewed proposals from three companies before awarding the contract to 3rd Stone Design, of San Anselmo, CA. During June and July of 2009, manufacturing options in the United States were evaluated and production quotes requested from both the current manufacturer and alternative United States manufacturers. Competitive bids from five United States manufacturers were received and analyzed. Activities during July and August 2009 focused on a scan of potential manufacturers in Brazil, China, and India. Production quotes from four companies in China and three in India were received and analyzed (we did not receive any quotes from Brazilian companies). Data from these quotes were used to design a materials forecast model for cost of goods/build at low-, medium-, and high-volume production. The final report was delivered in September 2009. It included analysis of the competitive bids, projections of production costs in the United States as compared to India and China, and an evaluation matrix of manufacturers. HealthTech now has solid options for manufacturing partners in China and India, in addition to competitive manufacturers in the United States.

Achievements and progress in the past six months

- Negotiated an agreement with 3rd Stone Design, a production engineering consulting firm, for a manufacturing review in the United States and three other countries.
- Developed an evaluation matrix of manufacturers to rank potential manufacturers according to key criteria.
- 3rd Stone Design conducted a site visit to the MRPC Corporation, the current contract manufacturer of the SILCS Diaphragm, in Butler, Wisconsin, to evaluate production capacity and costs.
- Developed a cost of goods (COGs) model based on the manufacture of the SILCS device at MRPC.
- Updated and refined the SILCS Diaphragm production and design engineering drawings in preparation for soliciting production quotes from alternate manufacturers.

- Identified potential alternative manufacturers in the United States that fit the required production profile. Fourteen companies with expertise in liquid silicone injection manufacturing were contacted, and 12 companies signed nondisclosure agreements. Bids were received and analyzed from five companies.
- Solicited potential manufacturing partners in Brazil, China, and India and requested production quotes from interested companies. Quotes from China and India were received.
- Used the production quotes to expand the COGs model to reflect production options inside and outside the United States, and at differing production levels.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

This project is complete.

HealthTech will seek funding for next steps required to ensure SILCS Diaphragm product supply. These steps include (1) a manufacturing review to refine the production procedures for scaled-up production and (2) due diligence with the chosen manufacturer(s) including on-site visits to verify production capacity and have discussions regarding pricing/tooling and distribution rights.

Development of a strategic global access plan for the SILCS Diaphragm

Goal of project

The goal of this project is to characterize market opportunities and introduction strategies for the SILCS Diaphragm in key developed and emerging markets.

This is the first step to laying the groundwork for a comprehensive market-launch strategy and preparedness plan. Data from this project will be used to guide commercialization and introduction planning during the next five-year period.

Status of project as of September 2009

HealthTech reviewed bids from three international research firms for this scope of work before awarding the contract to Quintiles Global Consulting. The market assessment included primary research with both reproductive health care providers and potential users; secondary research to establish the competitive landscape for barrier contraceptives in key countries; and recommendations regarding target populations, introduction strategies, and development of a revenue forecast model.

This market research will be the foundation of the value proposition used in negotiating with potential commercialization partners. It will also inform the direction for future formative market research such as consumer research for messaging in key markets, developing a framework to assess new markets, and evaluating distribution channels.

Achievements and progress in the past six months

- Reviewed proposals from three international firms for this work and awarded the contract to Quintiles Global Consulting to implement the market assessment.
- Held a project launch meeting in July 2009 to orient the Quintiles research team to the SILCS product, refine the work plan, and provide background about the SILCS Diaphragm, the barrier contraceptive market, and program and research resources.

- Quintiles and HealthTech staff completed the competitive landscape of the SILCS device relative to other barrier methods to inform product positioning and messaging.
- Developed comprehensive clinician-specific and consumer-specific discussion guides and a product profile of the SILCS device to test attitudes, assumptions, and potential interest in the SILCS device. Content of the clinician guide was pretested, tested, and refined before launching primary research interviews. Interviews were scheduled with reproductive health providers and potential users in the United States, Canada, and Western Europe (United Kingdom, Germany, and France) as well China, India, and Brazil.
- Adapted a consumer e-survey from the end-user interview guide and posted to US-based audiences.
- Quintiles presented an interim report in Seattle in September 2009. Quintiles will use feedback from the HealthTech team and other stakeholders to refine the assessment. The final market analysis report is expected in October 2009.

Problems encountered and actions taken to resolve them

Market assessments usually rely on a combination of both secondary and primary research to characterize the competitive landscape and assess the market potential for a new product. Since vaginal barrier methods, such as the diaphragm, represent such a small part of the competitive contraceptive market, they are not well captured in the sales and market share of reproductive health care products. Therefore, we decided to put greater emphasis on expanding the primary research interviews to capture preliminary impressions about the acceptability and interest in this new product. We also brainstormed alternative low-cost ways to recruit and solicit feedback from women who might be interested in the SILCS Diaphragm. This resulted in an abbreviated form of the in-depth interview being posted as an e-survey in the United States to gain additional insight about the potential cervical barrier market in the United States.

Since diaphragms are not currently available in emerging- or developing-country markets, we selected three countries in which to test potential interest. India was selected because it could become a manufacturing site. India recently hosted a consultation focused on reintroducing diaphragms, and there is a cultural suspicion of hormonal methods in India. China was selected because it is a potential manufacturing site and there is some indication of increased interest in contraceptive choice among young women. Brazil was selected because it has a locally manufactured diaphragm and a strong women's empowerment movement, both factors that could favor a future introduction of the SILCS Diaphragm. Lack of available information as well as limited funding for this project meant we were only able to obtain preliminary interest indicators in these countries. Additional research is needed to further characterize market opportunities.

Next steps and milestones expected in the next six months

- Quintiles and HealthTech will refine a final report of the SILCS Diaphragm market assessment. HealthTech staff will use findings from this market survey to develop the SILCS Diaphragm value proposition that will be used in negotiations with commercialization partners.
- HealthTech will seek additional funds to initiate consumer-focused market studies to further understand market opportunities and prepare for introduction planning through public and private channels.

SILCS Diaphragm over-the-counter strategies

Goal of project

The project goal is to develop a regulatory strategy for the SILCS Diaphragm as an over-the-counter (OTC) product and submit an application to the United States Food and Drug Administration (USFDA). The implications of an OTC product for introduction and marketing in various markets will also be explored.

Status of project as of September 2009

This project is composed of two parts. The first is to engage the USFDA to clarify expectations and data needed in support of a SILCS Diaphragm application for market approval as a nonprescription device so we can identify whether additional information is needed to satisfy USFDA requirements. We will develop a plan to obtain additional bridging data, if required.

The second part of this project is to begin characterizing the implications and tradeoffs of OTC for commercialization strategies in the United States and other key markets. The scope of this second activity will be contingent upon the outcome of the USFDA discussions and the level of funding available. We will leverage opportunities for collecting these data as part of other projects (i.e., pivotal study, SILCS Diaphragm gel delivery studies, and the SILCS Diaphragm market assessment) while waiting for the USFDA review of the investigational device exemption (IDE) amendment and a determination of whether an additional bridging study will be required.

Achievements and progress in the past six months

- Worked with a regulatory consultant to prepare an amendment to the SILCS Diaphragm IDE that reviews the evidence from previous clinical studies that the single-size SILCS device fits a broad range of women.
- Summarized the design and development history of the SILCS Diaphragm user instructions, including the results from user comprehension studies in South Africa, Thailand, and the Dominican Republic, which indicate the instructions are understood even by low-literate populations.

Problems encountered and actions taken to resolve them

Planning the SILCS Diaphragm regulatory application as a nonprescription device is new territory. No other currently approved diaphragm is available OTC due to the sizing issue. Also, neither Lea's Shield® nor FemCap® were submitted for OTC approval, so there is not clear precedent as to what data the USFDA will require when reviewing this application. HealthTech and CONRAD staff are working closely with the USFDA and regulatory advisors to develop the case.

Next steps and milestones expected in the next six months

- CONRAD is compiling the fit information from the pivotal study (95% of women participating were able to fit the device) and will add that to the IDE amendment. We plan to submit the amendment to USFDA by December. After USFDA reviews the OTC amendment, they will provide guidance as to whether an additional bridging study is needed to strengthen the case for approval as a nonprescription device.
- Submit the SILCS Diaphragm IDE amendment outlining the case for OTC based on available data expected from the pivotal study and request a pre-IDE amendment meeting (December 2009).
- Work with a commercialization officer to characterize implications of an OTC claim in selected markets.
- Opportunistically assess provider and other stakeholder attitudes, expectations, and questions regarding SILCS Diaphragm introduction in various markets.
- Seek funding to plan for introduction scale-up.

Element: Maternal and Child Health

Anemia etiology tool

Goal of project

The goal of this project is to initiate the preliminary phases of the development of an affordable point-of-collection device (POC) that will classify individuals' anemic status and elucidate the potential causes of anemia. The device has multiple potential markets, each of which will have their own specific requirements for device attributes. One of the primary goals during this concept stage will be to ascertain these requirements from informative interviews with stakeholders within each of the potential markets. More importantly, we will attempt to determine what minimal attributes of the device they are willing to accept, as the ultimate purpose of this device will be to meet the needs of multiple markets rather than a single market type. We will also be determining the technological feasibility of developing the proposed tool. The first phase of the feasibility assessment will center on the rough vision of the tool, and the second phase will become more detailed as we get feedback from the needs assessment of the various potential users of the device.

Status of project as of September 2009

HealthTech has successfully completed the first phase of the project. In determining the requirements of potential markets, we were able to develop product specifications that can meet the needs of multiple markets. The proposed device would have great impact as a screening tool in antenatal clinics to assess the impact of school de-worming programs, in primary health care centers, and in district hospitals for managing malaria and anemia. The device was not found to serve the needs of the malaria surveillance market, if it only contained hemoglobin and malaria indicators it would benefit malaria control programs. The proposed device does have the potential to serve the needs of the nutritional iron community for cross-sectional surveys if (1) an iron supplementation program actually existed, and (2) if the community could agree on biomarkers for iron status. It would not be useful for screening children prior to the administration of iron supplements because logistically it is not feasible to do so, nor would it be affordable. We have drafted the product specification for the most probable early adopter—antenatal clinics. The device would also meet the needs of surveillance workers for iron supplementation and school de-worming programs. We therefore decided to multiplex the antenatal panel onto an ELISA format to serve two purposes. Primarily, it will reduce research and development (R&D) resources needed to get all assays functioning under the same conditions so that they can then be transferred to the POC format. Secondly, it would serve as preliminary data that is essential for all R&D grant applications.

In the second phase, we have begun to assess the technological feasibility of the tool by screening companies that are the most likely to be able to translate their multiplexed platform into an actual prototype. The report on these companies and a summary of their platforms will serve as a template for us to answer the next major question in this feasibility exercise: can this proposed device be developed with any existing or emerging technological platforms, and, if so, who are the best candidates to build a consortium to develop it? This will be the primary focus for the next year, with secondary objectives to include hookworm biomarker discovery, validation of assay configuration, and market analysis.

Achievements and progress in the past six months

- Generated an illustrative visual representation of the proposed device; this illustration will be used for technical feasibility assessments and stakeholder interviews.
- Presented a concept poster at the Micronutrient (MN) Forum in Beijing. A one-page summary report of the meeting was drafted regarding stakeholders in the area of anemia and iron deficiency.
- Generated a report on the results of the hookworm diagnosis review; this report illustrates the potential biomarkers for antigen and/or antibody detection and potential partners for collaboration.
- Completed a summary analysis of in-country user needs assessments (UNAs) for Kenya and Zambia.

- Completed in-depth interviews with international stakeholders regarding iron biomarkers via telephone and in person at the Bangkok MN conference in September 2009; a report is pending.
- Produced a product specification sheet for an integrated and multiplexed device for the early adopter market.
- Compiled a short list of potential companies capable of integrating platforms, multiplexing immunoassays on a POC format, and separating blood from serum within a device.
- Contracted Quansys to configure multiplex assay conditions for iron status, inflammation, malaria, HIV, and syphilis.
- Identified hookworm and HIV-infected sera for use in R&D of early prototypes.

Problems encountered and actions taken to resolve them

We were unable to obtain permission for the Tanzanian stakeholder interviews from the Tanzanian Ministry of Health. We targeted Tanzania because of the work on iron deficiency in malaria-endemic areas being conducted in Pemba, Tanzania. Given the nature of the activity, there has no clear path for government approval as there is for clinical research. Our letter of intent appears to have been lost in the bureaucracy of the Tanzanian Ministry of Health. Meanwhile, we found very similar responses from the Kenyan and Zambian UNAs, and therefore feel that there is no need for additional UNAs.

We received conflicting reports on the utility of certain iron biomarkers for the purposes of cross-sectional surveys and the screening of children prior to the administration of prophylactic iron supplements. Based on these disparate responses, we decided to conduct in-depth interviews with leading experts in this area. We were able to interview experts on iron status biomarkers for both clinical diagnosis and population-based surveys. Although it is not clear which biomarkers are the preferred method, we did learn that all biomarkers are affected by inflammatory response. Therefore, no matter which biomarkers we choose, we must measure C-reactive protein and acid glycoprotein.

We also discovered that there is consensus that more data is required to determine which iron biomarkers are appropriate for malaria-endemic areas. Current studies in Kenya, including one through a National Institutes of Health (NIH) grant, are hoping to answer this very question. We will closely monitor the research groups in this area and engage them to aid in product development in terms of validation of biomarkers as well as obtaining samples for R&D of the prototype.

In mid-summer, the project's commercialization officer left PATH to pursue a career in medicine. We were able to complete our UNA activities by bringing on an infectious disease physician working at PATH to perform the interviews with the Kenyan health care provider interviews. PATH recently hired a replacement commercialization officer for the project with in-depth experience in moving medical devices from concept stage to the market.

We encountered a conflict of interest with hookworm researchers when we tried to obtain antigen and antibody pairs for the multiplex assay configuration experiment. Members of the team had a conflict of interest related to specific proteins for use as a diagnostic, and we were not able to obtain the reagents for our initial experiment. Through a third-party collaborator we were able to determine that the leader of the research group, who is a leading advocate for tropical anemia, called a group meeting to discuss ways in which this conflict of interest can be navigated. The group appears to be open to collaboration but must first find a way to work with each other that will not also put other projects at risk. We identified other research groups to work with if this group fails to find a way forward with PATH.

Next steps and milestones expected in the next six months

- Identify a bioengineering consultant and negotiate contract terms for an in-depth look at potential commercial partners capable of meeting our product specifications.
- Initiate a market analysis of early-adopter markets and begin the development of a global access plan.

- Scrutinize the short list of companies to ascertain which will provide a consortium capable of developing an affordable prototype.
- Approach selected companies with the concept and determine their willingness to collaborate.
- Navigate conflict of interest issues with the hookworm researchers and approach other partners capable of collaborating in the discovery of hookworm diagnostic biomarkers.
- Begin validation of the multiplexed assay from Quansys with existing ELISAs.
- Follow up on iron biomarker in malaria-endemic areas with organizations that were awarded NIH funding and develop partnerships for obtaining samples for validating R&D aspects of prototype development.
- Continue assessment of other biomarkers used in ascertaining the etiology of anemia such as hematological and novel biochemical indices that could be adapted to a POC format.

Chlorhexidine for umbilical cord care

Goal of project

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

Status of project as of September 2009

CHX product supplied by the local manufacturer was delivered successfully to operations research (OR) study sites in Sylhet, Bangladesh. An introduction plan for the introduction of the CHX product in Bangladesh is being revised and strengthened based on OR study results and input from stakeholders.

Achievements and progress in the past six months

- Negotiated and signed a memorandum of understanding between PATH and Popular Pharmaceuticals Ltd. (Popular) to specify roles of each party in relation to the upcoming OR study.
- Worked with Popular to complete compatibility and stability tests that allowed the product (with a nine month shelf life) to be released for research purposes only.
- Worked with Popular to facilitate delivery of the product for the OR study per a prearranged batch delivery schedule including development of a mold for the primary container.
- Finalized a subcontract with Dr. Ziaul Islam, Associate Scientist at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR-B), for a demand assessment using the contingent valuation method.
- Continued formula optimization work with Frontage Laboratories, including compatibility and stability testing with the plastic primary container for the CHX product.
- Developed instruments for stakeholder interviews and focus group discussions in the public and private sectors (ministries of health [MOH], key doctors, medical professional organizations, nongovernmental organizations [NGOs], United Nations Children's Fund [UNICEF], etc.), which will be used to develop better understanding about CHX and Clean Delivery Kit use and their packaging individually and together.
- Worked with Research Training and Management International (RTM) to conduct the initial stakeholder interviews and focus group discussions, and facilitated RTM's ability to conduct initial discussions with international donors and NGOs based in Bangladesh (UNICEF, Saving Newborn Lives, USAID), that could be included in stakeholder interviews.
- Developed a preliminary product introduction framework that includes the six components: (1) product, (2) price, (3) place (i.e., distribution), (4) promotion (product promotion, behavior change communication [BCC], etc.), (5) policy, and (6) people (i.e., training).
- Liaised with USAID to follow up on submission to the World Health Organization Essential Medicines List.
- Developed an introductory document for global scale-up of the CHX product.
- Participated in the results dissemination workshop for the OR project organized by the Projahnmo group in Dhaka at the end of September 2009.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Conduct a demand assessment study, analyze data, and report final results to partners.

- Continue our collaboration with RTM to develop a draft product introduction plan for the CHX product in Bangladesh that includes the six components: (1) product, (2) price, (3) place, (4) promotion, (5) policy, and (6) people.
- Submit a final report of stakeholder interviews and focus group discussions in public and private sectors.
- Plan and conduct stakeholder workshops with key policymakers (MOH, key NGOs, etc.) to review and vet the draft product introduction plan.
- Plan and conduct informational workshops with key medical professionals to review and vet the draft product introduction plan.
- Arrange stakeholder visits to Sylhet, as needed.
- Negotiate and sign a commercialization agreement with Popular.
- Assist Popular in the submission of regulatory applications to the Bangladesh Directorate of Drug Administration, as needed.
- Collaborate with Popular to launch the CHX product in key Bangladeshi markets, as appropriate.
- Revise the plan for global scale-up of the CHX product.
- Liaise with CHX efficacy trials funded by the Bill & Melinda Gates Foundation (Zambia and Pemba).
- Identify a market research firm that can conduct a global landscape analysis through a request for qualifications process.

Gentamicin in the Uniject[®] prefilled injection device

Goal of project

The goal of this project is to create a sustainable supply of gentamicin in the Uniject[®]¹ prefilled injection 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 September 2009

The field evaluation of gentamicin-Uniject in Nepal is complete; preliminary analysis suggests that using gentamicin-Uniject as part of community-based management of neonatal sepsis is feasible and acceptable to health workers and the community. HealthTech and the Argentine pharmaceutical manufacturer, Instituto Biologico Argentino (BIOL) are working to develop and compile the data and expert opinion in support of a future submission by BIOL to the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), the Argentine drug regulatory agency, for registration of gentamicin-Uniject. BIOL has inventory of the appropriate empty Uniject device and gentamicin raw materials for production of additional supply if required.

Achievements and progress in the past six months

- Traveled to Nepal to conduct final data collection activities for a field evaluation in July 2009. Preliminary data analysis was conducted and submitted to USAID with a trip report in August.
- Facilitated acquisition of empty Uniject devices and gentamicin raw materials for future production of gentamicin-Unijects at BIOL.
- Created a working draft of the manuscript to document resolution of critical technical feasibility issues for gentamicin-Uniject (in collaboration with a consultant identified by Rodney Ho at the University of Washington School of Pharmacy).
- Traveled to Zambia to assess a potential site for field evaluation of gentamicin-Uniject in August. The assessment was contained in a trip report submitted to USAID in September.
- Communicated with Dr. Anita Zaidi in Pakistan about the possibility of a gentamicin-Uniject field evaluation.
- Attended a neonatal sepsis meeting in Dhaka, Bangladesh, in September 2009, to assess potential opportunities for field evaluation of gentamicin-Uniject at the Save the Children/United Nations Children's Fund neonatal sepsis study site.

Problems encountered and actions taken to resolve them

Planning for the consultative meeting to discuss current data on sepsis treatment and its application to the value proposition for gentamicin-Uniject is currently on hold per guidance from USAID. HealthTech continues to wait for USAID confirmation to resume planning of this event.

Identification of an appropriate location for another field evaluation of gentamicin-Uniject has been challenging. We will continue to work with our colleagues at USAID to identify an optimal site.

Next steps and milestones expected in the next six months

- Submit a manuscript, in collaboration with BIOL, on compatibility/stability test results of the gentamicin-Uniject product for publication in a peer-reviewed journal.
- Conduct a rapid assessment of value exercise for gentamicin-Uniject.
- In collaboration with colleagues in Nepal, finalize the report of the Nepal field evaluation of gentamicin-Uniject. The report will be disseminated in Nepal at a meeting in January 2010.

1. Uniject is a registered trademark of Becton, Dickinson and Co.

- Submit an abstract to the Global Health Council 2010 annual meeting about the Nepal field evaluation of gentamicin-Uniject.
- Submit at least one article about the results from the gentamicin-Uniject field evaluation in Nepal for publication in a peer-reviewed journal.
- Identify an appropriate site for a second field evaluation of gentamicin-Uniject preferably in sub-Saharan Africa.
- Participate in the coordination of the proposed second-stage field evaluation in Nepal, when appropriate.
- Commission BIOL to produce another batch of gentamicin-Uniject: if the need for additional supply and appropriate funding is identified, BIOL will continue stability studies for future use in a registration dossier.
- Monitor ongoing community-based studies designed to reduce neonatal mortality and the international policy debate regarding possible changes in standard treatment guidelines for neonatal sepsis (examples of this would be the inclusion of oral antibiotic with gentamicin-Uniject or switch therapy).
- Finalize an expert opinion document summarizing rationale and justification for the specific dosing indications for registration of gentamicin-Uniject. This will enable BIOL to complete the regulatory documentation necessary for their application to ANMAT for registration of gentamicin-Uniject, a key step on the path to eventual commercial availability.
- Engage key stakeholders in a consultative meeting to discuss current data on sepsis treatment and its application to the value proposition for gentamicin-Uniject when appropriate.
- Based on the outcome of the consultative meeting, develop guidance for the most appropriate scenarios/settings for using the gentamicin-Uniject product.

Intradermal vs. intramuscular delivery of influenza vaccine in immunocompetent elders

Goal of project

Intradermal (ID) administration of influenza vaccine shows promise as an alternative to intramuscular (IM) injection, the current standard of care. ID 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 hypothesized that in older individuals a reduced dose of influenza vaccine given by the ID route may achieve the same degree of protection. We also postulated 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 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 September 2009

HealthTech sponsored a study with funding provided by the National Vaccine Program at the Centers for Disease Control and Prevention through USAID. Working with the Veterans Affairs Puget Sound Health Care System and Vanderbilt University, the project team sponsored 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 years and over. Study results were provided in previous status updates. The team is awaiting finalization of the study manuscript for publication in the *Journal of Clinical and Infectious Diseases*.

Achievements and progress in the past six months

- Investigators gave a poster presentation at the American Geriatrics Society Annual Meeting April 30, 2009, in Chicago.
- T-cell assays were completed. T-cell response revealed low interferon-gamma and tumor necrosis factor-alpha expression by CD4 or CD8 cells following ID and IM vaccination.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Finalize and submit the manuscript to the *Journal of Clinical and Infectious Diseases* by October 31, 2009.

Neonatal resuscitation

Goal 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 September 2009

A market assessment of existing resuscitators, resuscitation mannequins, and suction devices in the Economic Community of West African States (ECOWAS) region is being finalized. Manuscripts of work that has been completed in India and Indonesia are being prepared for submission to peer-reviewed journals. Activities to increase demand for devices in the South African Development Community (SADC) countries by raising awareness of appropriate devices continue to be undertaken (with funding from another donor). Because the recent introduction of the low-cost resuscitator and resuscitation mannequin by the Laerdal Foundation will reconfigure the market for resuscitation devices, further project activities are being terminated.

Achievements and progress in the past six months

- Completed the final report from the situational analysis of essential newborn care (ENC) in selected states in India in collaboration with the government of India, USAID/India, World Health Organization-India office, United Nations Children's Fund, IndiaCLEN, and PATH's office in India. The report was printed and distributed to key stakeholders in India.
- Finalization of the results and recommendations from market research in the ECOWAS region are in process; the report will be submitted by the end of December 2009.
- Finished the manuscript on the Indonesia device evaluation; it will be submitted to an appropriate journal such as the *Journal of Perinatology*.
- Participated in a meeting of the American Association of Pediatrics Global Implementation Task Force in Baltimore on May 1, 2009.
- Collaboration continues with the on-going South Africa health systems strengthening project (funded by another donor) to raise awareness of the importance of neonatal resuscitator devices and the local availability of high-quality and affordable devices. The collaboration resulted in the development of two items: (1) a SADC region-specific guide to purchasing resuscitators that lists all high-quality, affordable devices identified in the market research and (2) a one-page advocacy brief that emphasizes the importance of neonatal resuscitation, millennium development goals, and information for how to order a high-quality, affordable device from interested distributors/manufacturers.

Problems encountered and actions taken to resolve them

Final preparation and submission of a manuscript to an appropriate journal on the Indonesia community-based asphyxia study that was conducted with other funding continues to take much longer than anticipated primarily because the main author is no longer employed by PATH and is busy with other engagements. We have a PATH staff person working with the author to facilitate the completion of the manuscript.

Next steps and milestones expected in the next six months

- Submit report of market research in the ECOWAS region by the end of December 2009.
- Prepare and submit a manuscript to an appropriate journal on the ENC study in India, if possible.
- Disseminate a summary of results and recommendations from the market assessment in SADC countries to key stakeholders as part of the policy brief currently being prepared after the dissemination workshop in Durban in late October (funded by another donor).

- Disseminate SADC region-specific guide to purchasing resuscitators via email to PATH contacts in the SADC region.
- Edit and submit a manuscript on the Indonesia community-based asphyxia study that was conducted under other funding to *Pediatrics* or other appropriate journal, if possible.

Oxytocin in the Uniject[®] prefilled injection device

Goal of project

The goal of this project is to improve and ease adoption of active management of the third stage of labor and thereby reduce postpartum hemorrhage by facilitating both competitive commercial *supply of* and public-sector *demand for oxytocin* in the Uniject^{®1} prefilled injection device (hereafter called oxytocin-Uniject).

Status of project as of September 2009

Instituto Biologico Argentino (BIOL) officially launched its oxytocin-Uniject product in Argentina during the summer of 2009 and had its first commercial sales. The product is now registered in Guatemala, and the company is initiating the registration process in several additional countries.

Several pilot activities introducing oxytocin-Uniject are underway or planned. Introduction activities are currently being implemented in Guatemala, and activities in South Africa are anticipated to begin in the fourth quarter of 2009. Interest is being expressed in a number of other countries, such as Nicaragua and the Dominican Republic. Activities planned for Honduras have been put on hold due to the political situation there.

Achievements and progress in the past six months

- Attended the Prevention of Postpartum Hemorrhage Initiative Working Group and Uterotonic Drugs and Devices Task Force meetings in April 2009.
- Participated in a panel and presented the oxytocin-Uniject work at the Global Health Council conference in Washington, DC, in May 2009.
- Provided technical assistance to BIOL to prepare for the World Health Organization (WHO) prequalification process. BIOL submitted a dossier to WHO in June of 2009 for prequalification of both oxytocin-Uniject and ampoule (10 IU) presentations.
- BIOL registered its oxytocin-Uniject product in Guatemala and officially launched commercial sales in Argentina.
- Shipped supplies of oxytocin-Uniject to Guatemala for introduction activities.
- Initiated pilot introduction activities in Guatemala, including training of health workers in use of oxytocin-Uniject for postpartum hemorrhage prevention in health facilities.
- Submitted a proposal through the PATH Nicaragua office to the USAID mission to support an introduction study of oxytocin-Uniject. HealthTech provided technical input to the proposal.
- BIOL submitted technical files for commercial registration in Honduras and Nicaragua. Registration is pending in those countries.
- Traveled to Argentina in September 2009 to work closely with BIOL to plan for a WHO good manufacturing practice inspection and to plan for wider product availability in 2010.
- Gland Pharma initiated stability studies and expects to have product available to support an Indian Council of Medical Research (ICMR) study in India by the end of 2009.

Problems encountered and actions taken to resolve them

The pilot introduction in Honduras has been delayed due to political unrest. The United States government has put a hold on all activities there.

1. Uniject is a registered trademark of Becton, Dickinson and Co.

Next steps and milestones expected in the next six months

- Complete pilot introduction activities in Guatemala including the implementation of a cost study.
- Participate in the Prevention of Postpartum Hemorrhage Initiative end of project meeting titled “Tackling the biggest maternal killer: Progress and challenges in preventing postpartum hemorrhage.”
- Develop a comprehensive product management/market development plan for oxytocin-Uniject with a Latin America focus.
- Submit an abstract to the 1st Latin American and Caribbean Conference on Global Health, which will be held in Mexico in April 2010. We may also submit an abstract to the Global Health Council for the annual meeting. We would like to share results of the pilot introduction in Guatemala in both of these venues.
- Assist with logistics of supplying oxytocin-Unijects for the pilot in South Africa.
- Continue to develop information, education, and communication materials on oxytocin-Uniject as needed to support broader uptake.
- Continue to provide support to BIOL in their efforts to obtain WHO prequalification.
- Provide technical assistance to BIOL as they work to improve their Uniject packaging and labeling operations for increased efficiency.
- Pending funding, explore the feasibility of establishing an oxytocin-Uniject production facility in Indonesia as requested by USAID.
- Continue to respond to inquiries from the field regarding potential introduction activities including Nepal and the Dominican Republic.
- Provide technical support to Gland Pharma to ensure availability of product for the ICMR study and another study in India to be implemented by the Bill & Melinda Gates Foundation-funded Oxytocin Initiative project.
- Provide technical support to BIOL to ensure availability of product for a study in Ghana to be implemented by the Gates Foundation-funded Oxytocin Initiative project.
- Pending funding, provide technical assistance to PATH Nicaragua on pilot introduction activities.

Rapid human papillomavirus antibody test

Goal of project

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

Status of project as of September 2009

Funding for the project was provided to HealthTech via USAID from the National Vaccine Program. Prototypical reagents for the test were obtained from the National Cancer Institute (NCI) and resulted in encouraging data that suggested moving forward with commercial-grade reagents. HealthTech is currently working on an agreement to secure these key reagents from commercial partners that will appropriately manage intellectual property contributed by all collaborators. Research and development of the test is on hold until key reagents can be obtained from commercial partners. Initial research on the test was promising with a limited sample set provided by NCI. A panel of characterized anonymized samples is in place for the development of the test.

Achievements and progress in the past six months

- Secured a royalty-free license for research use of key reagents from NCI. This agreement will allow PATH access to key reagents for development of the test.
- Continued to work with collaborators to develop the agreements necessary to access the reagents for the test.

Problems encountered and actions taken to resolve them

Slow response from collaborators providing critical reagents has hampered the ability to perform laboratory-based research. Discussions between the collaborators and NCI have revealed intellectual property hurdles. A multipronged approach to address these hurdles has been planned. HealthTech is actively working to secure research licenses for intellectual property to allow access to materials and reagents to assess the feasibility of the test.

Next steps and milestones expected in the next six months

- Secure commercially available antigen and assess its utility in the next generation prototype test.
- Evaluate the next generation prototype test with the panel of serum samples and identify any areas that need additional research and development.
- Create a plan for further research and development of the test, if needed.
- Identify strategies for production of small-scale prototype tests for further evaluation.

Retinol binding protein enzyme immunoassay

Goal of project

This project's goals are to enhance the reliability and ease of assessment of vitamin A deficiency (VAD) and decrease its associated cost. Specific objectives are to improve the consistency of results of vitamin A assessments, including ease of specimen analysis and interpretation, and to improve the reliability of VAD estimates.

Status of project as of September 2009

The retinol binding protein enzyme immunoassay (RBP-EIA) was successfully transferred to Scimedx a few years ago, but there have only been a few sales.

Achievements and progress in the past six months

- Completed an analysis of stalled product uptake.
- Sent a summary of findings to USAID.

Problems encountered and actions taken to resolve them

The major hurdle to adoption of RBP-EIA to assess vitamin A deficiency is the lack of World Health Organization (WHO) endorsement. We learned that WHO is forming a steering committee to review indicators for vitamin A and iron. We will discuss with USAID an investigation to understand the steps required for RBP to be officially recommended by WHO to program managers.

Next steps and milestones expected in the next six months

- Provide technical support to Scimedx as requested.
- Track the activities of the WHO steering committee and possibly investigate the steps required for RBP to be officially recommended by the organization.

Technologies to strengthen systems for immunization

Goal of project

The project goal is to improve developing-country immunization programs through development, assessment, and advocacy of technologies and systems. In particular we are focusing on:

1. Improving the ability of immunization program managers to monitor vaccine distribution systems, vaccine stock, and equipment allocations to ensure appropriate cold chain capacity and vaccine safety through improved cold chain management information systems (cold chain MIS).
2. Identifying, developing, evaluating, and introducing alternative technologies for refrigeration and other cold chain functions to help extend the reach and security of immunization programs (cold chain technologies).
3. Strengthening immunization through technologies for safer and more effective vaccine administration (immunization safety).

Status of project as of September 2009

The immunization delivery technologies project team has been active across three focus areas—cold chain MIS, cold chain technologies, and immunization safety. The project team has been shifting priorities over the past year to focus more on the cold chain areas and less on immunization safety. This report will identify a number of immunization safety accomplishments that were met during this reporting period, and moving forward, the work of this team will focus only on two key areas—cold chain MIS and cold chain technologies.

We continue to work collaboratively with the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) on a number of different fronts including the development and revision of Performance, Quality, and Safety (PQS) requirements; the development of the Cold Chain Equipment Manager (CCEM) software program; informing and contributing to the Project Optimize body of knowledge and strategy; and participating in Safe Injection Global Network (SIGN) and TechNet global meetings.

Achievements and progress in the past six months

Cold chain MIS

- Hired a software engineer in May 2009 to complete rigorous testing of CCEM Version 2.0.
- Developed a partnership with two other PATH initiatives, Project Optimize and the Rockefeller Foundation-funded Collaborative Requirements Design Methodology Project; these two projects are providing co-funding for development of CCEM 2.1.
- Contracted the services of a Seattle-based software development firm in August to complete the necessary design, coding, testing, and user interface improvements to deliver a validated version of a CCEM software tool developed with Microsoft Access 2007. The final product—CCEM Version 2.1—will be delivered on October 31, 2009.
- Drafted a use case catalog that outlined the system behavioral requirements by detailing scenario-driven threads through the functional requirements for CCEM.
- Worked closely with a PATH user interface expert to determine how to improve the usability and graphic design of CCEM; the team routinely relayed this information to the software development firm for implementation.
- Corresponded with representatives from the African Regional Office as well as the Kenya UNICEF, EPI, and WHO staff to plan for the testing of CCEM in Kenya early in 2010.

Cold chain technologies

- Completed a basic phase change material (PCM) landscape for the Twinbird Stirling cooler refrigerator. Various design analyses and experiments have been conducted with regard to meeting

PQS holdover time. Two PCM liner configurations were developed that meet the PQS holdover time—both designs require no manufacturing change to the current Twinbird product.

- Over the last six months, data was collected on all additional tropical locations included in the World Radiation Data Centre database with at least a five-year record of ground-based measurements. These data will accompany the solar autonomy calculation tool.
- Drafted the PQS language enabling the inclusion of the solar autonomy calculation tool as a normative reference: the preliminary draft has been submitted to WHO.
- Participated in the SolarChill partners meeting in Geneva in July 2009. This meeting brought together WHO, UNICEF, the Danish Technical Institute, Greenpeace, GTZ Proklima.org, PATH, the United Nations Environment Programme, Vestfrost, and Brightlight Solar to discuss how the partnership can better coordinate to introduce direct-drive solar vaccine refrigerators. One noteworthy outcome of this meeting is the pending approval of US\$2.7 million to the consortium from World Bank Global Environment Facility (GEF) funds to support field evaluation and technology transfer of the SolarChill vaccine refrigerator (which is currently manufactured by Vestfrost).
- Developed a proposal for a hybrid refrigerator for vaccine cold chain storage. The refrigerator specifications include a long holdover time via optimized use of insulation and phase change materials, electric grid autonomy through the use of low-cost photovoltaic panels and new battery technologies, and low system costs via minimal-maintenance Free Piston Stirling Cooler technology.

Immunization safety

- Tested the water vapor transfer rate (WVTR) of one specific single-dose reconstitution device configuration with multiple film barriers. An initial analysis of placebo vaccines for evaluation of hygroscopic characteristics necessary for a robust WVTR stability test was completed and a final placebo vaccine powder was selected. Protocols for stability testing were completed. The team fabricated, filled, and sealed 540 test devices and then initiated a 6-month test with all of these devices.
- Two members from the HealthTech team traveled to Hyderabad, India, in September to train health care workers on the use of an adapter for intradermal (ID) injections and to gather feedback on acceptability and usability of the device based on simulated use. Based on the feedback received during their visit, the team is refining the protocol for the use of this device during a clinical trial in mid-2010 and is also drafting formal reports for distribution to key partners including Indian Immunologicals Limited and West Pharmaceuticals. Follow-on work is funded through leveraged funding.
- Sent information on the Hopkins Needle Cutter (the Cutter) design including PATH's design improvements to Sol-Millennium Medical Products Co., Ltd. in China. PATH is no longer actively seeking manufacturers interested in the Cutter but is open to sharing the design with potential future interested parties that express an interest.
- Continued efforts in collaboration with the Making Medical Injections Safer project, to support the production of high-quality safety boxes in Africa and identify a local manufacturer with the potential to meet WHO PQS standards. Safety boxes from two Kenyan and one Ethiopian supplier were tested by a materials consultant at the University of Washington. The consultant used paper board testing procedures to translate WHO's performance specifications (i.e., water resistance, puncture proof) into technical paper specifications (i.e., burst strength, density, and grammage). These technical specifications were shared with the Kenyan and Ethiopian manufacturers of safety boxes along with contact information for companies who sell high-grade paper board. HealthTech drafted a report on the work and will be disseminating it in advance of the SIGN/PQS meetings in December 2009.
- HealthTech sent a representative to meet with Omani Ministry of Health officials, WHO, and EPI program managers to demonstrate and collect feedback on the use of the HealthTech-developed plastic spike produced by Star Syringe and combined with their Auto-Disable reconstitution syringe

for measles vaccine reconstitution. WHO has incorporated the plastic spike reconstitution syringe in an aerosolized measles study currently underway in India.

Problems encountered and actions taken to resolve them

Cold Chain

In May 2009, PATH contracted a software testing consultant to review the stability and to develop a testing protocol for CCEM prior to anticipated field testing of CCEM in Kenya in July. Feedback received from the consultant, in combination with findings by PATH staff, clarified that CCEM 2.0 had not undergone sufficient rigorous testing and was not sufficiently stable for wide release as a cold chain inventory management and planning tool. It was decided that while CCEM 2.0 met all the functional requirements identified in the initial scope of work, the program required redevelopment using standard software engineering methodologies to ensure stability and user acceptance for widespread cold chain equipment planning. We have hired a software engineering firm that is using a rigorous process to capture requirements and to document these requirements in a tightly structured fashion through a “use case” methodology. The anticipated outcome of this effort is to have CCEM 2.1, a stable software application based on CCEM 2.0, pretested in Kenya at the end of 2009 and ready to be used for a country-wide cold chain inventory in January 2010. To complement local technical support, it is expected that CCEM 2.1 will be hosted on an open-source forum managed by Microsoft staff to encourage an open venue for sustained technical support for CCEM 2.1.

Immunization Safety

Initial placebo (mannitol-based) vaccines tested in the single-dose reconstitution device were not sufficiently hydrophilic to provide the water absorption resolution needed for a robust test. The team had to spend considerable effort and time developing an alternative approach and finally selected trehalose to represent hydrophilic vaccines. Initially the team thought that mass change would be a sufficient method to use for measuring water absorption but later realized that an alternative titration method (the Carl Fischer test) would be necessary to provide the sensitivity level needed.

The first iteration of injection molded ID adapters was analyzed in a user assessment by nursing students in Hyderabad, India. As this was the first batch of adapters produced with the new material and process, inconsistencies were not surprising. The adapters brought to India did not match the device specifications and were therefore not functional. Warping of various pieces of the device caused the needle to deflect upwards and prevented it from puncturing the skin layer of the model arm. In order to solve this problem, the ID adapters were trimmed and sanded in the field. The needle no longer deflected toward the ID adapter and was able to puncture the model skin correctly.

Next steps and milestones expected in the next six months

Cold chain MIS

- Complete the development of CCEM Version 2.1 by October 31, 2009.
- Introduce CCEM for pilot adoption in two countries by March 2010 (Kenya and potentially Vietnam).
- Continue to promote and advocate for use of CCEM in global venues including at the Eastern and Southern Africa regional WHO EPI managers meeting in 2010.
- Develop the associated promotional and training materials for CCEM Version 2.1.
- Define the specifications for a web-based CCEM Version 3.0.
- Develop (with joint funding from UNICEF) an open-source mobile data collection platform to support the baseline cold chain infrastructure survey data collection application. A prototype will be designed, tested, and iterated by Sustainable Sciences Institute in collaboration with the PATH office in Nicaragua and is expected to be completed by early December.

Cold chain technologies

- The HealthTech team is leveraging non-HealthTech funds for the continued work with Twinbird engineers to turn the Stirling cooler refrigerator prototype into a manufactured product. The team anticipates WHO PQS qualification of the Twinbird in the next six months.
- Continue work to encourage the use of solar refrigeration technologies for the immunization cold chain.
 - Draft the final report on the solar autonomy calculation tool for inclusion in the WHO PQS equipment standards for solar-powered vaccine refrigeration systems as a normative reference. Completion of the final report is expected by the end of 2009; initial release to industry is expected in early December.
 - Participate in multiagency planning for the World Bank GEF project to implement a large-scale demonstration of SolarChill vaccine refrigerators in Colombia and Kenya. With a downstream objective of technology transfer to local manufacturers, PATH will provide expertise in vaccine refrigerator technical evaluation and collaboration with private industry, as well as ensure the active engagement of ministries of health in all stages of program implementation.
- HealthTech leveraged funding for a team member to attend the SIGN and PQS consultative meetings in Geneva in November 2009 to discuss accomplishments and learn about other efforts in the area of cold chain technologies.

Immunization safety

- The HealthTech team is deferring efforts related to immunization safety and will seek alternate funding to further this work.

Element: HIV/AIDS

Advancing prevention technologies for sexual and reproductive health

Goal of project

The goal of this project is to accelerate development and introduction of multipurpose technologies that prevent pregnancy, sexually transmitted infections, and other common reproductive tract infections.

This project builds on momentum generated through planning and implementing the Advancing Prevention Technologies for Sexual and Reproductive Health symposium held in March 2009, where over 140 participants from 11 countries participated. Presentations outlined the need and opportunity for multipurpose prevention technologies to better address reproductive health needs of couples in both developed and developing countries. Researchers, policymakers, and funding agencies outlined a plan of action to raise awareness and bring this initiative to a larger audience.

Status of project as of September 2009

HealthTech is helping coordinate follow-up activities from the symposium. These include organizing a strategic advisory committee meeting to develop a plan for next steps and developing and producing a briefing/advocacy document to make the case about the need for multipurpose prevention technologies, including an outreach plan for distributing the document after it is printed.

Achievements and progress in the past six months

- Organized a follow-up meeting in July 2009, of the symposium's Strategic Advisory Group where working groups reported results from the mapping exercises describing status of current and future multipurpose prevention technologies.
- Chaired one of the working groups and worked with group members to articulate the mission of this sexual and reproductive health initiative. The group brainstormed short- and long-term priorities for inclusion in the funding case.
- Led the development of the strategic outreach plan and the purpose and intent sections for the "making the case" briefing document. The briefing document is in process. Revisions of the first draft are underway by HealthTech. The manuscript will be sent to the advisory committee for external review in late October.
- Other related activities in support of this initiative include:
 - A symposium proceedings report was distributed electronically to symposium participants and other relevant audiences.
 - A website has been developed posting the symposium presentations.
 - Advisory committee members have used national and international meetings, such as the Association of Reproductive Health Professionals conference and the Alliance for Microbicide Development meeting, to publicize the conference website and the upcoming briefing document as well as solicit feedback from health care providers and policymakers about next steps.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Complete first draft of the briefing document. Coordinate external review and revisions process (November 2009).
- Finalize the briefing/advocacy document including layout, graphics, etc (December 2009/January 2010).
- Develop talking points to help introduce the briefing document (January/February 2010).

- Develop outreach so the briefing document and other project resources can be used by a broader coalition of stakeholders in discussions with researchers, product developers, policymakers, funding agencies, and reproductive health program advocates (February/March 2010).

Microbicide applicator project

Goal of project

The goal of this project is to ensure that safe, appropriate, affordable delivery devices for microbicides are available for use in low-resource settings.

Status of project as of September 2009

HealthTech is advancing feasibility research on two dual-purpose prevention options (SILCS Diaphragm controlled-release and PATH Woman's Condom [WC] plus microbicide films). HealthTech is planning to initiate two clinical studies in the coming year: one to evaluate safety of the modified paper applicator (with Profamilia in the Dominican Republic), and one to conduct a feasibility study of the controlled-release SILCS Diaphragm to assess performance, acceptability, and safety (with the California Family Health Council in California).

Achievements and progress in the past six months

- Selected, with USAID, Tenofovir for the comparative safety study to be conducted by the Contraceptive Research and Development Program (CONRAD) based on product availability, timeline, and budget. The comparative safety study protocol has been finished and the institutional review board reviews have been initiated at PATH and in the Dominican Republic.
- Participated in the World Health Organization/Joint United Nations Programme on HIV/AIDS's technical consultation on Preparing for Access to PRO 2000 and incorporated applicator bridging studies into the priority activity list.
- The University of Pittsburgh, Magee-Womens Research Institute (MWRI) Pharmaceuticals Group started conducting studies to assess the compatibility of an existing quick dissolve film formulation previously developed by the Pharmaceuticals Group at MWRI (using UC-781) with the PATH WC.
- Continued work with Queens University of Belfast (QUB) on the fabrication of drug-loaded SILCS Diaphragm spring cores with specific achievements including: CONRAD provided an additional 400 grams of UC-781 to QUB for further research and development (R&D) work; polyoxymethylene (POM) copolymer has been selected as the preferred material for fabrication of the spring core component of the microbicide-releasing SILCS Diaphragm device owing to its processability at temperatures below 200°C, its similar mechanical performance to nylon 6.6, and its ability to provide sustained release of UC781; QUB fabricated the first round of UC781-loaded intact spring cores to send to the MRPC Corporation (the SILCS device manufacturer for silicone overmolding). These fully intact drug-loaded spring cores will provide increased accuracy in future in vitro release testing.
- In vitro studies at QUB have demonstrated: (1) UC781-loaded POM copolymer pellets overmolded with LSR9 silicone elastomer provides controlled zero-order release of UC781 and (2) the UC781 release rate from reservoir-type systems is dependent upon UC781 loading.

Problems encountered and actions taken to resolve them

The fabricated spring cores sent by QUB to the MRPC Corporation for overmolding have required additional adjusting to the molds at MRPC. Representatives from QUB and PATH met at MRPC to review and troubleshoot the overmolding process.

Next steps and milestones expected in the next six months

- Initiate the comparative safety study of the modified paper applicator in the Dominican Republic.
- QUB will conduct (1) stability testing, (2) mechanical testing, and (3) in vitro release testing on intact SILCS devices, loaded with 1, 5, and 10 percent UC781 into POM spring cores.

- Install and optimize a precision liquid injection molding technology at the Medical Polymer Research Institute at QUB (a facility jointly supported by the Schools of Pharmacy and Mechanical Engineering). Develop and optimize appropriate manufacturing methods to provide various test batches of microbicide-loaded SILCS Diaphragms in house at QUB for more rapid design iteration and testing.
- Commission a number of new molds from a QUB machine shop. These molds will be suitable for spring production on the Morgan Press and will greatly increase the capability of QUB Pharmacy engineers to undertake material assessments.
- Establish an agreement with the California Family Health Council to conduct a feasibility study of the controlled-release SILCS Diaphragm to assess performance, acceptability, and safety. Draft the study protocols and related materials.

PATH Woman's Condom—technology transfer

Goal of project

The goal of this work is to ensure that a supply of high-quality Woman's Condoms (WCs), produced by a commercial manufacturer using good manufacturing practices, will be available to begin multiple clinical studies to support regulatory submissions. We anticipate several years of intensive manufacturing, regulatory, and clinical activities with the ultimate goal of registering the device in China, Europe, and the United States and making it available for international procurement and introduction in HIV/AIDS and sexual and reproductive health programs.

Status of project as of September 2009

HealthTech's work with Shanghai Dahua Medical Apparatus Co. (Dahua), the current manufacturer of the WC, is moving forward. Dahua has worked on advancing the production processes and making decisions about raw materials, finalizing a physical testing specification now filed with the local government, and working with PATH and local research partners on preparing protocols and obtaining ethical clearances for the first clinical trials of the devices. Our timeline is stretching somewhat with current plans for approval by the Chinese State Food and Drug Administration (SFDA) in the first half of 2011. PATH continues to seek additional funding from USAID as well as others to keep this project moving forward.

Achievements and progress in the past six months

- HealthTech researchers traveled to Shanghai in June to train the in-country research teams on the focus group discussion (FGD) and couples use study protocols. The teams were led by Dr. Wu Junqing at the Shanghai Institute for Planned Parenthood Research (SIPPR) and Dr. Zirong Huang at the Fudan University Obstetrics/Gynecological Hospital.
- The FGD research to familiarize researchers and the community with the device was approved by the PATH Research Ethics Committee (REC) and the SIPPR Ethics Review Committee in August 2009. The study was initiated in collaboration with SIPPR immediately upon receipt of these approvals. Data collection is currently underway with nine potential user segments.
- Based on information from the SFDA, the clinical trial plan was revised. The current plan is to conduct a non-comparative couple's use study (40 couples with four uses each). PATH and Dahua are investigating with SFDA if the results of this study could possibly be submitted for market registration. The protocol for this study has been developed, reviewed by external sources including the Contraceptive Research and Development Program and received contingent approval from the PATH REC and the SIPPR Ethics Review Committee. The protocol is currently pending ethical approval at the Fudan University site.
- Completed a request for proposal (RFP) process to identify and select a market research firm to conduct a market evaluation and segmentation study; we are currently finalizing an agreement for work to start at the beginning of November.
- Conducted a technical meeting in Shanghai between HealthTech and Dahua in September. The production status was reviewed, and plans for clinical trial production runs were developed.

Problems encountered and actions taken to resolve them

Feedback from participants in the June training and from the formative research revealed that there may be acceptability issues with the lubricant sachet packet. Dahua is investigating alternative packaging options (the alternative package may not be ready in time for the first clinical trials in China, which is expected to launch in December 2009). The formative research also indicated that Chinese women may not find applying the lubricant with the finger acceptable. The research team will explore strategies for making the lubricant application more acceptable.

At the request of Dr. Huang, Principal Investigator of the Fudan site, HealthTech compiled a background document outlining the rationale/justification for a performance and failure mode study for female condoms. Since Fudan University Obstetrics/Gynecology Hospital is a certified research site for clinical trials of new contraceptives, she was concerned that the ethics committee might refuse to review the proposed study since it is not a contraceptive-effectiveness study, which is the type of study they would have expected. After reviewing the documentation HealthTech compiled, the ethics committee agreed to review the proposed performance and failure mode study for the WC.

At this stage of the technology transfer there are some challenges in determining the best timing for various improvements to the production line. The main question is whether to keep pilot-process steps in place for clinical trial production runs or start to develop a more scaled-up process ahead of the clinical trials. This is complicated somewhat by the fact that Dahua is in the process of building a new factory where the final WC production line will be staged. With HealthTech's concurrence, Dahua has decided to begin clinical trial production on current pilot-scale equipment, adding a few machines for cap and lube production in late 2009. These machines will then need to be relocated to the new facility when it is ready in mid-2010. We have engaged condom production consultant, Mr. Bill Potter, to visit Dahua in the fourth quarter of 2009 to help evaluate these technical decisions and help Dahua understand the steps needed to move their production to International Organization for Standardization and United States Food and Drug Administration standards.

Next steps and milestones expected in the next six months

- Convene a global-level strategic advisory group to advise on WC launch and global introduction strategies.
- We expect to receive funding from a third party to help support Dahua's purchase of new equipment for scaling up the lubricant and dissolving cap production.
- Completion of final sourcing of raw materials; the first articles will be available from the Dahua assembly line using all their own materials. HealthTech will perform bench tests in Seattle to confirm the quality of the product.
- Production validation at Dahua through visits by HealthTech staff and a condom production consultant.
- Dahua is expected to produce inventory for the China clinical trials as well as for two clinical trials in the United States, scheduled for early 2010.
- Initiate a couple's use study of the WC at two sites in the Shanghai area.
- Begin the RFP process in fourth quarter of 2009 for market research related to Chinese-specific positioning and branding strategies for the WC using a total market approach of combining public and private sectors.
- Begin development of a China product introduction plan for the anticipated late 2010 launch.
- Preliminary results from the market evaluation and segmentation study will become available in March 2010.

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

Goal of project

The goal of this study is to assess the acceptability of the SILCS Diaphragm as a microbicide delivery system during couples' use. Couples will evaluate two gel application scenarios and compare use of these to acceptability when microbicide gel is delivered by a vaginal applicator. The outcome of this project will be two-fold: (1) to identify women's preferred scenario for gel application and (2) 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.

Status of project as of September 2009

The study protocol received final approval by the PATH Research Ethics Committee (REC) and the California Family Health Council (CFHC) institutional review board (IRB) in July. Study implementation began immediately. After the first month of study, HealthTech staff and the research team submitted a study protocol modification to both respective ethics committees to increase the number of clinicians participating in the study and the number of screening sites to ensure the study target goal would be met on schedule. The modification was approved, and the clinical portion of the study is on target to be complete by December 2009.

Achievements and progress in the past six months

- Approval given by the PATH REC and the CFHC IRB for the protocol and related study documents in July and the study was launched.
- Developed and submitted a protocol modification increasing the number of physicians and the number of sites eligible to screen and enroll couples. The modification was approved in August, and by September enrollment rates had improved for this study.
- By September, CFHC had enrolled half of the couples approved for this study. The research team already had scheduled pre-enrollment visits and enrollment visits for a sufficient number of couples to likely cover the remaining recruitment during the next month.

Problems encountered and actions taken to resolve them

Within the first month of the study, the research team identified that they needed additional staff to screen couples and an additional site to allow evening screening enrollment visits for couples who had passed through prescreening. A protocol modification was drafted. Once approved, this helped ensure that couples who were approved through the prescreening process were more likely to follow through with enrollment visits and be screened into the study. The study is on target to complete the clinical portion by late November or December.

Next steps and milestones expected in the next six months

- Complete implementation of the clinical portion of the protocol.
- Complete follow up focus group discussion with a subset of women who complete the study.
- Analyze the qualitative and quantitative study results.
- Draft final report. Identify opportunities to share study results with relevant audiences.

SILCS Diaphragm microbicide delivery system assessed through MRI

Goal of project

The goal of this study is to assess the feasibility and acceptability of the SILCS Diaphragm as a microbicide delivery system. Using magnetic resonance imaging (MRI), this proof-of-concept study will assess retention and dispersion of a microbicide gel to the cervix and vaginal canal when delivered by the SILCS Diaphragm compared to the dispersion and retention when the gel is delivered by a standard vaginal applicator. Scans will be taken before and after simulated intercourse and after six hours of product wear to mirror current guidelines for diaphragm use. Women will assess acceptability of the different gel delivery systems via microbicide delivery system acceptability scales. The candidate microbicide BufferGel[®], manufactured by ReProtect, will be the gel in this study.¹

Status of project as of September 2009

The main study was completed in June 2009. Analysis of the qualitative data from the acceptability surveys and the in-depth interviews began in July and is expected to be completed by November. Analysis of the MRI scans began in July, but currently is on hold, pending approval of a modification request for a few additional MRI scans to help interpret the data. Once approved, the additional study procedures should be completed in about one month.

Achievements and progress in the past six months

- The main study procedures, randomized crossover comparison of three gel delivery modes with MRI, and qualitative assessments was completed in June 2009, by all six women.
- The research team outlined additional MRI scan procedures in a protocol amendment that was submitted to the University of Pennsylvania (U Penn) and PATH internal review boards (IRBs) in September.

Problems encountered and actions taken to resolve them

The U Penn research team encountered difficulty interpreting the MRI scans. Scans where women used a SILCS Diaphragm to deliver the BufferGel showed much less gel in the vagina than scans where women delivered gel via a vaginal applicator. We expected some difference in gel volume, but not to the degree found on the scans. The research team hypothesizes that women may not have inserted the expected volume of gel when using the SILCS Diaphragm. During the study, some women reported difficulty handling the sachet packets and loading gel onto the SILCS Diaphragm.

The modification requests approval to call back two to three of the study participants for an additional series of MRI scans. Women in Part 3 of the study will load the gel using a prefilled applicator to ensure that the correct volume is loaded and inserted on the SILCS Diaphragm.

We are not sure whether a thin layer of gel would have clinical implications. However, the protocol amendment will allow us to assess whether the discrepancy of gel volume shown on the MRIs could have resulted from women not loading expected volume onto the SILCS Diaphragm, losing gel outside the introitus during insertion, or losing gel when she checked placement of the SILCS device after insertion (i.e., expected volume not present in vagina at time of first MRI).

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

Next steps and milestones expected in the next six months

- Implement additional MRI scans after amendment is approved by both IRBs.
- Analyze MRI data set and interpret findings.
- Complete analysis of qualitative data sets.
- Draft report of study findings.
- Draft manuscript of study findings, if appropriate.
- File study closure documents with IRBs.

Skunkworks

Diagnosics

Enhancement of the immunochromatographic strip test—europium technique

Many point-of-care strip tests suffer from poor sensitivity or sensitivity that is not adequate to make the test clinically useful. PATH is developing a fluorescent detection system for strip tests that should improve sensitivity of tests. To date, we have developed a europium latex conjugate that can be excited using a simple ultraviolet (UV) light source and emits in the visible spectrum. We also are developing a simple, handheld reader for this fluorescent approach that combines inexpensive charge-coupled device 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.

We discovered that sales of the *Chlamydia trachomatis* antibodies we used in our first generation system were discontinued by the manufacturer (Dako Inc.). We then conducted a comprehensive literature search for new antibody candidates and carried out a lab-based evaluation of their utility for our system. Through this process we selected a set of antibodies. We have resumed evaluation of antibody conjugation, wash buffers, and sample preparation and antigen lysis. In the coming six months we expect to continue with this line of research in an effort to optimize the capture and detection conditions. In parallel, our commercial partner (Axxin Inc., formerly Fluidyx Inc.) will provide updated software and technical service, along with initiating research on locating and evaluating miniaturized components for an eventual handheld device. PATH will evaluate the underlying technologies for the handheld device against commercially available benchtop analyzers.

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. Current filter paper-based collection efforts are limited by the high concentration of PCR inhibitors (e.g., red blood cells on the membrane surface). Therefore, only a small fraction of a specimen can be used in the assay or complex, expensive methods are employed to remove inhibitors.

PATH 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. It 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.

During this reporting period, we have performed design work to develop an appropriate form factor for the device. This work has been greatly influenced by a user needs assessment performed in South Africa. Our goal is to create a design that maximizes ease-of-use for the health care provider collecting the specimen as well as for the laboratory staff who will perform the assay. We are designing the device so that it could be used to prepare specimens for point-of-care testing or to support existing centralized testing networks. In addition to this design work, we have developed protocols and procured materials, instruments, and reagents that will allow us to rapidly evaluate and optimize design iterations to achieve adequate performance in the laboratory.

RPA assay for infant HIV

Early investigation into the isothermal DNA amplification technology known as recombinase polymerase amplification (RPA) assay shows that it may have great potential for use as a point-of-collection assay for the diagnosis of infant HIV and many other infectious diseases. So far, PATH has performed genome-wide analysis with up to 338 different HIV-1 sequences to screen for suitable targets with which to develop an HIV-1 RPA assay that can detect all subtypes of HIV-1. Highly conserved regions in the *gag*, *pol*, and long terminal repeat regions have been identified, and we are currently working with our commercial partner, TwistDX, to establish exactly which targets will be chosen to design the new assay. Of note is that the proof-of-concept assay based on a subtype B sequence reacts with similar sensitivities on subtype A and D HIV strains even though there are several polymorphisms in the target DNA sequence with these subtypes. The limit of detection with accurately quantitated HIV-1 DNA is 3 copies per reaction, comparable with the best real-time PCR assays. An internal control targeting a human DNA sequence has been designed for multiplexing with the HIV-1 assay. This is a notable first for isothermal assays where typically only the diagnostic assay is performed and the development and integration of an internal control is a very important addition. This also demonstrates reagent efficacy and specimen integrity within the same diagnostic test, if the specimen is negative for HIV.

We have studied the effects on inhibitory compounds on the preliminary RPA HIV-1 assay and discovered that the assay can tolerate 10% of whole blood or 3% of hemolysed blood being added directly to the reagents and run in the reaction. In addition we have found that the assay can tolerate up to 2% of nonionic detergent in the test reaction. These are very important considerations for the design of a very basic, yet rapid and effective specimen preparation method. We are developing a specimen collection method by using a product from another PATH project that has designed a membrane to purify and concentrate infected T lymphocytes from a small blood sample (e.g., a heel prick). The membrane can be placed directly into the RPA assay, and HIV-1 DNA is detected from this. This method is currently undergoing optimization.

All isothermal reactions need a basic heater to incubate the reaction. At PATH we have demonstrated in a series of experiments that we can heat RPA assays using an exothermal chemical compound rather than an electrically powered heater. The test data from these experiments have shown that the results from chemical as opposed to instrument incubation were 100% identical. We are using both lateral flow strips and a fluorescence reader to ensure more than one platform is available as a diagnostic tool with the RPA assay. By using the T lymphocyte capture card in conjunction with basic extraction and chemical heating with lateral flow strip detection of amplicons, we have demonstrated in-house the first entirely power-free nucleic acid amplification system which could be used at point of care in resource-limited settings.

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

The aim of this technology development effort is to develop diagnostic technologies that extend access and reduce cost to viral-load testing in low-resource settings. Specifically, under this funding and with external co-funding, we have developed an entirely PATH-controlled technology that allows extraction of RNA for clinical specimens at second- and third-tier health care facilities. The technology addresses two challenges in viral-load testing: (1) it complements emerging low-cost, low-complexity nucleic acid amplification platforms, both isothermal and PCR based; and (2) it removes the stringent requirement of cold chain in centralized viral-load testing systems.

We have undertaken two activities:

- A detailed cost analysis of the whole process of viral-load testing in a low-prevalence country (Nicaragua). This report has allowed us to concretely identify the technology opportunities and specifications that can make viral-load testing more efficient and affordable.

- Sourced and performed stability studies on a panel of packaging options that will make this a viable low-cost product. Packaging and storage of reagents and materials is a major and chronically underestimated challenge in diagnostic product development.

PATH is currently seeking funds to transfer nucleic acid extraction technologies, including this one, to regional diagnostic test producers in Africa in order to make nucleic acid testing more affordable.

Immunization

Fast dissolving tablets for oral immunization

For several diarrheal disease vaccines in the pipeline, each will contain several live bacterial or viral strains. There are no commercialized vaccines with such complexity today. It is a manufacturer's nightmare to develop a multivalent live attenuated bacterial vaccine, particularly for infants who cannot swallow a capsule or tablet. PATH is developing a fast-dissolving tablet formulation that can be manufactured using standard vaccine production technology. The tablet will disintegrate instantly in the presence of a small amount of saliva (without the need for water) and is suitable for both infant and adult use. Another advantage of this technology is the compact packaging, which is important with the limited cold chain capacity in many developing countries. We are working with Oregon Freeze Dry Incorporated to develop this technology and aim to apply the technology to diarrheal disease vaccines and tuberculosis vaccines through collaboration with the Enteric Vaccine Initiative and later on with Aeras Global TB Vaccine Foundation.

We evaluated buffer and pH for making the tablet formulation during this period. Since the pH range of vaccines must be held within a permissible range during the production process, 15 buffers were evaluated for compatibility of the enterotoxigenic vaccine at 4°C, 25°C, and 37°C. Of these, four buffers were selected for further analysis to determine the optimal pH range for the vaccine. The lyophilization process for preparing fast-dissolving tablets requires freezing the buffered vaccine, which causes a shift in pH. Using a universal pH indicator, the pH shift for various buffers under freezing conditions (-80°C and -20°C) was measured, and we discovered that phosphate buffer dropped two pH units (pH 7 to pH 5) while Tris (pH 8) and citrate buffer (pH 4) held steady. It was observed that the rate of freezing had little to no effect on this shift. Our next steps involve the preparation of a freeze dried tablet containing live vaccine. This proof of concept study with a single bacterial strain (vaccine) will be performed at Oregon Freeze Dry Incorporated, in Albany, Oregon.

Management information systems for immunization

In July 2009, the final report was made available for this collaborative effort by VillageReach and PATH to identify strategic approaches and key requirements for the successful development of Management Information Systems (MIS) in the last mile of immunization programs. This project evaluated the VillageReach MIS2 application, developed and implemented in Mozambique, in order to identify how a rational Health Management Information Systems design approach enabled an application that could be universally applied across health systems development. The final report provided a set of recommendations for VillageReach to use to further develop information systems for a broader audience in understanding the dynamics of investments in information systems at the last mile for public health. The key findings from this report were presented by co-author and chief technology officer for VillageReach, James Dailey, at the seventh annual Public Health Information Network Conference in Atlanta, Georgia, on August 30, 2009.

Thermosensitive gel formulation for sublingual immunization

Currently, there are no subunit vaccines given via a mucosal route because of the lack of appropriate formulation and delivery technologies. PATH has developed a formulation that is liquid at room temperature, but instantly changes to a gel at human body temperature. The gel is retained at the application site (for example, the inside of the cheek) for 30 minutes or longer to allow the vaccine to enter the immune system. The formulation can be applied easily with a dropper. The formulation also contains a potent and safe mucosal adjuvant (PATH has a license to this adjuvant for use with all vaccines related to global health projects), which augments the efficacy of the vaccine. We hope to further develop this technology by collaborating with the Enteric Vaccine Initiative (PATH) and Walter Reed Army Institute of Research.

During this reporting period, we have developed formulations which show liquid to gel transition in the range 35°C to 40°C, simulating the temperature inside the oral cavity. These formulations consist of a surfactant, mucoadhesive agent and a penetration enhancer. The surfactant protects the vaccine from enzymatic degradation while the mucoadhesive agent and the penetration enhancer help in increasing the residence time by assisting in the permeation of vaccine through the mucosal regions. These thermoreversible formulations have been tested in vitro in human saliva for their liquid to gel transition, and the mucoadhesive characteristic has been confirmed by the mucin binding studies. Our next steps for the team include testing these formulations in vivo (small animal model) for their thermoreversible transition and also to evaluate the immune response of selected vaccine formulations delivered through different routes (oral, rectal, and vaginal) in small animals.

Maternal and Neonatal

Automated blood pressure measurement device calibration

In low-resource settings, blood pressure measurements are often unreliable—if taken at all. Recently, in an effort to correct this, several manufacturers have developed low-cost, battery-powered, robust, automated blood pressure measurement devices. Reportedly these devices perform well but tend to drift out of calibration frequently. In the absence of proper, reliable calibration equipment, and processes, the accuracy of each individual low-cost device is unknown, and its usefulness as a diagnostic tool is questionable. We have been collaborating with a University of Washington student group, Vietnam Medical Clinic, sponsored by Wellness Global Foundation to conduct an informal blood pressure needs assessment focusing on calibration challenges in three clinics in Vietnam. While conducting research on calibration techniques, we have engaged key stakeholders, such as Dr. Mendis with the World Health Organization (WHO) who is Director of WHO's Affordable Technologies for Primary Healthcare group. We are tracking the clinical evaluation of multiple portable blood pressure instruments to identify the scenarios of use where a calibration tool for a blood pressure measurement device might have greatest impact. Recently we submitted a collaborative NIH Small Business Innovation Research (SBIR) proposal with Clinical Dynamics Corp. The SBIR proposal was not approved, but we continue to maintain regular updates and communication with this team and look for opportunities to cooperatively seek funding.

Noninvasive anemia screening

HealthTech is assessing how we might move existing noninvasive anemia screening technologies into a more feasible realm for use in low-resource settings and/or to identify feasible product development pathways for noninvasive methods. We will be engaging a consultant to assess the potential for current products that use spectrophotometry to become affordable and requirements for optimizing the products' use in low-resource settings. In particular, we are assessing near-infrared tomography based on either transmission or reflective spectroscopic data for their potential as an integrated strategy for a point-of-care

device. Currently, we have identified a consultant at Johns Hopkins University to undertake this work and are finalizing the contract with him.

We also identified a group in Texas that is working on the development and commercialization of a noninvasive optoacoustic platform which has many diagnostic applications. The University of Texas Medical Branch (UTMB)-based startup, Noninvasix (<http://www.houstontech.org/en/dir/1175/>), is focused on the development of the noninvasive system for measurement of hemoglobin concentration using a US\$250,000 grant from the Texas Emerging Technology Fund. The director of the Laboratory for Optical Sensing and Monitoring, Center for Biomedical Engineering, Department of Neuroscience and Cell Biology, and Department of Anesthesiology, at the UTMB in Galveston, Texas, informed us that they had initially received US\$50,000 funding from UTMB and are also planning on submitting a letter of interest to the Bill & Melinda Gates Foundation for further development of this technology.

“PremiePak” of life-saving interventions in mid-level resource settings for improved care for premature births

Creating a package of underutilized interventions with a strong evidence base such as low-cost pulmonary surfactant, betamethasone, and emerging lung support technologies for use in lower-resource settings can improve outcomes for preterm infants. PATH, in collaboration with the Seattle Children’s Research Institute, is exploring the feasibility of such a PremiePack of interventions, both bundled into one tool bag and as stand-alone interventions. Current activities focus on using the summary from the Global Alliance to Prevent Prematurity and Stillbirth meeting that was held in Seattle in May 2009 as a base for the identification of relevant interventions (behavioral practices and any complementary equipment). A white paper may be produced that provides details (current best practices, gaps in practice, commercial availability of equipment, etc.) for each specific intervention. Once the set of specific interventions have been identified, optimal operational pathways for low-resource settings will be determined. Testing the acceptability and feasibility of PremiePack interventions in a mid-level resource setting will be critical to demonstrate the usefulness of this approach.

Urethral plugs for fistula treatment

HealthTech conducted a global landscape analysis of existing mechanical devices, with emphasis on urethral plugs, used to treat stress urinary incontinence (SUI) following obstetric fistula repair. From the landscape analysis and interview with experts, the *FemSoft*[®] Insert (Rochester Medical Corporation, USA) urethral plug was identified as the most promising baseline technology for introduction into a low-resource setting to meet the needs of women with SUI post-fistula repair. The *FemSoft*[®] Insert is currently the only available mechanical device that is being used to treat SUI post-fistula repair in developing countries.

Based on the interviews and literature research, product specifications were developed and design changes of urethral plugs to treat SUI post-fistula repair in low-resource settings were identified. The main recommendations from the report are:

- Conduct a user assessment in two African countries. This assessment will provide direct information from women who use the device to fully understand how it can be improved to serve the needs of this population. The user assessment would also serve as an opportunity to explore alternate solutions to treat this problem such as absorbent underwear (such as Depend[®] products) in both reusable and disposable form or sanitary pads in both reusable and disposable form.
- Perform design modifications of the existing device to meet the product specifications required for the treatment of SUI post-fistula repair.
- Strengthen the dialogue with the Rochester Medical Corporation regarding a joint venture to perform design modifications of the urethral plug device to adapt its use to low-resource settings.

OTHER

Developing a systematic architected rational approach for design of information and communication technologies

Information and communication technologies (ICT) have tremendous potential to enable, support and sustain stronger health systems in low-resource countries. Health systems will become stronger when management processes, skills, and tools are adopted that are appropriate and sustainable. Today the availability of appropriate, effective, and sustainable tools to deliver information for local health management is severely limited. We believe a major reason is the lack of systematic, architected, and rational approaches (SARA) to the design, development, and implementation of ICT systems and solutions. PATH is forming a community of practice around SARA to advance methods, resources, and tools that will serve as a catalyst for ICT innovation.

Our investigation of methods and tools has lead to several promising candidates that we have adapted to better meet needs in global health. Chief among the most promising methods is the ability to gather and document end-user requirements by engaging users in a facilitated requirements workshop. This method has been applied in developing requirements in vaccine logistics, tuberculosis case detection, and HIV case documentation with encouraging results. Our next steps for SARA are to continue to validate and refine the requirements-gathering process while also advancing the documentation of requirements for use with software developers and stakeholders. In addition, we will be validating the effectiveness of these requirements in specific projects in the coming months, involving the design, development and deployment of ICT solutions that address specific health programs in the field.