

HealthTech IV

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Highlights and milestones of HealthTech projects during the past six months

- In close coordination with Family Health International (FHI), HealthTech advanced the development of training materials for the use of depo-subQ provera 104™ injectable contraceptive in the Uniject® prefilled injection device in support of planned acceptability studies in selected USAID-priority countries.
- The SILCS Diaphragm team submitted an abstract to the World Health Care Congress entitled SILCS Diaphragm: New design in barrier protection. It was accepted for inclusion as part of the poster exhibit at the Highly Affordable Health Innovations Conference, April 12–13, 2010, in Washington DC.
- An amendment to the SILCS Diaphragm investigational device exemption application was drafted and reviewed by our partner. The amendment outlines the case for why the United States Food and Drug Administration should consider the SILCS Diaphragm as an over-the-counter product.
- The Anemia Etiology Tool team successfully multiplexed malaria, HIV, and syphilis on the assay platform configured by Quansys. They have now begun work on multiplexing iron and indicators of inflammation.
- The Chlorhexidine team completed chlorhexidine formula optimization work with Frontage Laboratories, including compatibility and stability testing with the plastic primary container for the product.
- An abstract was submitted to the Global Health Council 2010 annual meeting about the Nepal field evaluation of gentamicin in the Uniject® prefilled injection device. This abstract was accepted and Jaganath Sharma, one of the study principal investigators, will present the results on Tuesday, June 15, 2010, 10:45 am to 12:30 pm.
- HealthTech sponsored a study 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. The manuscript from this study was e-published in *Clinical Infectious Diseases* on April 8, 2010. <http://www.ncbi.nlm.nih.gov/pubmed/20377407>.
- HealthTech became an implementing partner of the Global Development Alliance (GDA): Management of Birth Asphyxia. We will work to strengthen logistics systems and to create/increase demand for newborn resuscitation devices by working in close collaboration with Laerdal Medical AS. We created a schematic for overall market development for the Laerdal products through the GDA including pathways for each of the implementing partners.
- The Oxytocin in Uniject team completed a facility-level pilot introduction of oxytocin in the Uniject® prefilled injection device in Guatemala in the fall of 2009 in close collaboration with the USAID-funded Prevention of Postpartum Hemorrhage Initiative, the USAID mission, the Guatemala Ministry of Health (MOH), and other in-country stakeholders. Results will be disseminated at a stakeholders meeting conducted by the Guatemala MOH, including a discussion and evaluation of the prospects for potential national scale-up in that country.
- Instituto Biológico Argentino has continued to drive forward registration of oxytocin in the Uniject® prefilled injection device in Latin America. In addition to registrations already obtained in Argentina and Guatemala, they have applied for product registration in seven other Latin American countries: Bolivia, the Dominican Republic, Honduras, Nicaragua, Paraguay, Peru, and Uruguay.
- The World Health Organization announced the establishment of a committee to address biomarker indicators for both population-based surveys as well as for diagnostic application. Results are due in December 2010. This decision is key to uptake of the RBP-EIA immunoassay.
- The services of a Seattle-based software development firm were contracted by HealthTech in August to complete the necessary workflow changes, systematic code updating and management, end-to-end testing, and user interface improvements to deliver a validated version of a cold chain equipment

manager (CCEM) software tool developed with Microsoft Access 2007. The final product—CCEM Version 2.1—was delivered on December 2, 2009.

- The cold chain technologies team developed a work plan, timeline, and budget to complete two objectives of the SolarChill consortium. Objective 1 is to define the local and regional market size and value for SolarChill refrigerators; evaluate SolarChill refrigerators in the field, and create a commercialization plan for a regional manufacturer. Objective 2 is to transfer the SolarChill technology to capable and interested companies in Colombia and Africa.
- The Health Information Systems team reviewed and disseminated the systematic, architected, and rational approach (SARA) as well as accompanying methodology for the design and development of health information systems in resource-constrained settings to project collaborators, the International Organization for Standardization Technical Committee 215 Joint Work Group, at a meeting in Bellagio, Italy.
- Proof-of-concept studies in collaboration with the University of Pittsburgh, Magee-Womens Research Institute Pharmaceutics Group, and CONRAD that illustrate the feasibility of anti-HIV drug incorporation into the PATH Woman's Condom capsule were completed. These studies specifically demonstrated that UC-781 can be formulated into the condom capsule. Two prototype UC-781-containing capsule formulations were developed and tested. Placebo formulations were compared against the currently used capsule.
- Shanghai Dahua Medical Apparatus Co., the current manufacturer of the PATH Woman's Condom, completed final sourcing of raw materials, and the first products from their assembly line became available. HealthTech performed bench tests in Seattle and confirmed the quality of the product and product quality was positively verified by testing at FHI in North Carolina.
- As part of the couples' acceptability of alternate gel scenarios study of the SILCS Diaphragm as a microbicide delivery system, a focus group was held with a subset of the female participants to assess study findings and investigate use patterns and acceptability. The qualitative results provided insights into how women in the United States would like to receive information about the SILCS Diaphragm, as well as points that appeal to them about the SILCS Diaphragm, and packaging.

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 March 2010

During this recent reporting period we have continued to monitor updates on the status of the several different efforts underway to bring a lower-cost version of the LNG-IUD to market.

Achievements and progress in the past six months

- In February, HealthTech received information about the new initiative sponsored by the social enterprise pharmaceutical company, Medicines360, and Uteron Pharma of Belgium. This collaboration, which was announced in late 2009, reports that recruitment for a Phase III clinical trial in the United States with a levonorgestrel-releasing intrauterine system (LNG20) is underway. The study is registered at the clinical trials.gov website: <http://www.clinicaltrials.gov/ct2/show/NCT00995150?term=medicines360&rank=1>.
- If this study is proceeding as announced, this group has moved to the forefront of the other initiatives. This group says their product could be launched by 2014.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Collect additional data about the Medicines360/Uteron LNG-IUD.
- Characterize the target cost point that would be considered reasonable by agencies for including an LNG-IUD in commodity procurement programs.
- Profile countries where introduction of LNG-IUD would be feasible according to established health infrastructure and health needs.
- Compile analysis and draft final report.

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 March 2010

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 has ramped up an expanded coordination role in the development and implementation of the USAID work plan for global rollout of the product. This includes convening partner meetings, project managing and coordinating the project, planning and implementing communications, and liaising with key implementation partners. HealthTech is also leading the development of training materials for acceptability studies planned for Malawi and eventual global rollout. Key activities currently planned or underway by planning and implementation partners for depo-subQ provera 104 in the Uniject device include a pharmacokinetics (PK) study for subcutaneous administration in the upper arm; an acceptability study in Malawi; demand modeling; logistics research; in-depth introduction planning for five countries including Kenya, Malawi, Pakistan, Rwanda, and Senegal, and other activities.

Achievements and progress in the past six months

- Convened and facilitated a meeting in Washington DC in December 2009, with partners who are actively involved with planning and implementing the product rollout, to document current progress of ongoing activities and identify key activity gaps and collaborative opportunities for consideration.
- Initiated planning for the next semiannual introduction planning Partner Working Group meeting to be held in Washington, DC, in May 2010.
- Based on partner input, prepared a comprehensive, multi-partner work plan for the USAID global rollout of depo-subQ provera 104 in the Uniject device, including designation of responsible organization and identification of the critical path for project implementation. Tracked critical path activities.
- Developed and launched a SharePoint site to facilitate up-to-date access by planning and implementation partners to project announcements, timelines, meeting materials, research findings, country-level introduction planning information, product references, and other information in support of introduction planning activities.
- Supported finalization of product configuration and access for the acceptability study in Malawi.
- Leveraged the activities of PATH's Introduction of depo-subQ provera 104 in Uniject project, funded by the Bill & Melinda Gates Foundation, to expand information gathering, partner collaborations, and communications at both global and country levels.
- Facilitated bimonthly coordination teleconferences with USAID and monthly teleconferences with Pfizer.
- In close coordination with Family Health International (FHI), advanced the development of training materials in support of planned acceptability studies in selected USAID-priority countries.

¹ depo-subQ provera 104 is a trademark of Pfizer.

² Uniject is a registered trademark of BD.

Problems encountered and actions taken to resolve them

In late 2009, 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^{®3} will be considered by Pfizer as an off-label use for the subcutaneous product. A PK study is planned to begin in the second quarter of 2010 to demonstrate the bioequivalency of administration of the subcutaneous product in the upper arm as a precursor to beginning acceptability studies in Malawi.

Next steps and milestones expected in the next six months

- Continue to act as the coordinating liaison among Pfizer, USAID, BD, and the planning and introduction partners to ensure effective communication, coordination, and timely availability of the product for acceptability studies and global rollout. Identify and communicate critical path milestones to USAID and other select stakeholders.
- Monitor and document expected registration and scale-up timing and communicate as needed across stakeholder groups for planning purposes; analyze risks and develop contingencies related to registration and product supply.
- Complete training materials for depo-subQ provera in the Uniject device in the acceptability studies that FHI will conduct in Malawi in 2010.
- Participate in and/or facilitate periodic phone conferences and meetings with Pfizer and BD for updates on regulatory status, manufacturing scale-up, and resolution of any product technical challenges.
- Coordinate with Pfizer for supply of initial quantities of product for use in acceptability studies planned for Malawi, as well as for additional acceptability studies that may follow.
- Facilitate discussion and clarification of product configuration issues (secondary packaging, inserts, possible bundled disposal boxes, etc.) and explore options to best optimize the product for various scenarios of use (i.e., in community-based distribution programs, via social marketing channels, etc.).
- Contribute as needed to the development and implementation of a PK study conducted by FHI related to upper arm subcutaneous injections.

³ Depo-Provera is a registered trademark of Pfizer.

SILCS Diaphragm commercialization

The next four 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:

- Devise a communication strategy for diaphragms.
- Evaluate the commercial market for the SILCS Diaphragm, including distribution channels, to develop a strategic global access plan.
- Complete a health system assessment for the introduction of the SILCS Diaphragm in a low-resource setting.
- Assess the regulatory and commercialization implications of over-the-counter distribution in the United States and other markets.

Communication strategy for diaphragms

Goal of project

The goal of the project is to coordinate with donors, researchers, women's health advocates, and other stakeholders to identify key research, communication, and advocacy needs to prepare for SILCS introduction. Specific project objectives are to identify the steps needed to advance diaphragms/cervical barriers for women's health and to explore the communication strategy and advocacy messages needed to raise awareness among women, the reproductive health community, and donors regarding the role of diaphragms for contraception.

Status of project as of March 2010

HealthTech is using strategic opportunities as they arise to share information about the SILCS Diaphragm and get feedback from potential commercialization partners and reproductive health advocates and other stakeholders to help hone SILCS Diaphragm messages needed for introduction. For example, in October 2009, the HealthTech SILCS Diaphragm team developed a commercialization brief that was presented as part of a packet of PATH materials at an international female condom meeting in Amsterdam. This provided an opportunity to get a SILCS Diaphragm update in front of a different audience of donors and reproductive health advocates. The commercialization brief also became part of the introduction packet sent to potential commercialization partners. HealthTech developed an abstract that was accepted as part of the World Health Care Congress' Highly Affordable Health Innovations poster exhibit. Staff will attend the Microbicides 2010 meeting, as will many researchers, advocates, and other stakeholders who are key to our project (and in conjunction with work related to the Initiative to Advance Multipurpose Prevention Technologies) rather than organizing a stand-alone meeting.

Achievements and progress in the past six months

- Developed the SILCS Diaphragm commercialization brief; this document has served as part of the introduction to potential commercialization partners.
- Met with donors (USAID and CONRAD), potential research partners (including the Centers for Disease Control and Prevention), and potential advocacy groups such as the Global Campaign for Microbicides as part of the cooperating agencies meeting in Washington, DC, in January 2010. While there, we discussed the strategy/opportunity for a study of the SILCS device's impact on protection from gonorrhea and chlamydia, research issues such as feasibility of SILCS use without contraceptive gel (if no alternative to N-9 spermicide is available at time of introduction), and the feasibility and safety of recommending the SILCS Diaphragm for continuous use wear to reduce barriers to use.
- Submitted an abstract to the World Health Care Congress entitled SILCS Diaphragm: New design in barrier protection. It was accepted for inclusion as part of the poster exhibit at the Highly Affordable Health Innovations Conference, April 12–13, 2010, in Washington DC.

Problems encountered and actions taken to resolve them

We originally proposed organizing a face-to-face strategy meeting with donors, advocates, and researchers that would have been held in conjunction with the Global Health Conference in May 2009. Since funding for this project was not awarded until Fall 2009, we revised the project to focus on coordinating communication among these key stakeholders to identify communication and advocacy needed to prepare for a SILCS Diaphragm introduction.

Next steps and milestones expected in the next six months

- Develop a strategy of advocacy and communication for the SILCS Diaphragm to raise awareness about this new product; identify key target populations and characterize communication needs.
- In conjunction with reproductive health advocates and potential commercialization partners, continue to refine key messages to raise awareness about the SILCS Diaphragm and solicit potential partners for next steps toward the SILCS Diaphragm's introduction.
- Continue to respond to opportunities to strategically share information about the SILCS device.

Development of a strategic global access plan for the SILCS Diaphragm

Goal of project

The goal of this project was to characterize market opportunities and introduction strategies for the SILCS Diaphragm in key developed and emerging markets. This was 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 March 2010

HealthTech contracted Quintiles Global Marketing to assess current markets (and potential new markets) for diaphragms in key developed and developing countries. This market research is part of the value proposition used to engage potential commercialization partners. This project has been completed.

Achievements and progress in the past six months

- Quintiles Global Marketing presented the draft final report of their research findings to HealthTech staff in December 2009 and submitted a narrative executive summary in January 2010. This work involved 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.
- Quintiles identified recommended next steps for formative market research such as conducting consumer research for messaging in key markets, developing a framework to assess new markets, and evaluating distribution channels. They assessed the market in developed countries where diaphragms currently are available (Canada, United Kingdom, United States, etc.). They also conducted a preliminary assessment of the potential market in a few target countries where diaphragms are not available (India, China).

Problems encountered and actions taken to resolve them

Since diaphragms represent only a very small portion of sales of family planning products, Quintiles had a difficult time finding sales information specific to diaphragms, even in developed-country market research sources. Diaphragms are not currently available in emerging- or developing-country markets. Therefore, some of the assumptions presented in the Quintiles global market assessment are based on very limited information. Additional research is needed to further characterize market opportunities.

Health Tech staff worked closely with Quintiles during the project to combine information we have collected about the market landscape for female barrier methods with the resources and analytical skills Quintiles brought to this project.

Next steps and milestones expected in the next six months

This project is complete.

SILCS Diaphragm health system assessment

Goal of project

The overall goal of this project is to assess feasibility and appropriateness of SILCS introduction in a low-resource setting. This project will characterize the regulatory pathway and policy regarding new contraceptive methods; the service delivery channels, logistics, supplies and health management information system for a single-size cervical barrier; the training needed to introduce this method; and the communications and advocacy needs for various audiences (health care providers, potential users, other decision-makers).

Status of project as of March 2010

We initiated this project with a short survey that we sent to key contacts in 11 countries to help assess potential interest in this health assessment and in considering future SILCS Diaphragm introduction. We received responses from nine countries, six of which expressed interest in being considered for this project. Based on a variety of factors, such as contraceptive use profile, unmet need for birth spacing, cultural factors that indicated a potential opportunity for future SILCS Diaphragm introduction, and interest among potential stakeholders, we decided to implement this study in Uganda.

We reviewed strategies and tools in the literature from health system assessments and reviewed tools from other projects planning the introduction of reproductive health products. We used these to develop the framework for the SILCS Diaphragm health system assessment.

Based on this background preparation, we developed a scope of work for an in-country consultant to implement the field evaluation. We identified two candidates who have experience in this type of formative assessment in Uganda. The field portion of the health system assessment is expected to occur from May through August 2010.

Achievements and progress in the past six months

- Investigated background literature and adapted tools and methodologies for use in this health system assessment.
- Developed a country interest survey and sent it to key stakeholders in 11 countries.
- Reviewed and analyzed the country interest survey responses. Identified two countries with characteristics that make a future SILCS Diaphragm introduction seem feasible and interesting. One of the two countries was selected due to funding constraints.
- Developed a scope of work and identified a potential consultant.

Problems encountered and actions taken to resolve them

Since this project was funded at half the level requested, we reduced the scope of work to implement the study in one country rather than two.

Next steps and milestones expected in the next six months

- Finalize the scope of work and sign the consultant agreement.
- Conduct desk research in preparation for field assessment.
Completed field assessment planning, identify potential user groups, and make key contacts for interviews, site visits, etc.
- The consultant will implement the field assessment.
- Complete a site visit to Uganda to assist with field assessment.
- Analyze data from the health assessment.
- Complete a draft report of key findings.

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 March 2010

Health Tech hired a regulatory consultant to assist in developing an amendment to the SILCS Diaphragm investigational device exemption (IDE) application that outlines the case for why the USFDA should consider the SILCS Diaphragm as an OTC product. This amendment reviews what evidence we expect to have at the time of the 510(k) application to show that the SILCS Diaphragm fits a broad range of women and that the instructions and proposed labeling for the SILCS device are easy to read and comprehend—even for women with low literacy. The HealthTech team outlined the fit data from previous studies and the data that is expected to become available after the results of the Phase II/III pivotal study are released. We also made a strong case that the evaluations of the SILCS Diaphragm instructions for use that were conducted throughout the design and development process go beyond what the USFDA usually requires for a label comprehension study. Still, the USFDA will review this application and determine whether an additional label comprehension study will be required.

This IDE amendment has been reviewed by several staff members at CONRAD. HealthTech is incorporating their final revisions. The IDE amendment is scheduled to be submitted to the USFDA in April. The USFDA should provide recommendations within a month about what additional bridging data is recommended for an OTC application.

HealthTech submitted a budget request to USAID for this study in anticipation that the USFDA will require a label comprehension study.

Achievements and progress in the past six months

- HealthTech and a regulatory consultant completed the draft IDE amendment.
- CONRAD reviewed the amendment and provided comments; the HealthTech team incorporated these comments into the amendment.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Awaiting the USFDA response to the IDE amendment.

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 informational 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 March 2010

We have completed the first phase of our feasibility assessment. During the first phase we collected information from stakeholders on the utility, desired product attributes, and a preliminary screen of potential platforms. Our project is midway through the second phase of determining feasibility; we are collecting detailed information on potential markets and more specific information on technologies capable of multiplexing on POC formats. The market assessment data will provide the information required to generate donor support as well as convince private-sector developers that this project is economically viable. We are generating dossiers on specific companies identified by our bioengineer as having the highest potential of successfully developing a product that meets our specifications. We will conduct preliminary due diligence to ascertain their candidacy as potential partners. The dossiers and due diligence information will be used to rank companies to approach for possible development partnerships.

Achievements and progress in the past six months

- The team's bioengineer assessed potential commercial partners capable of meeting our product specifications. Based on this assessment, we eliminated 20 of the 41 original companies with promising technologies and generated 3 dossiers describing the technology three selected companies and their potential to produce a product that meets our specifications.
- Designed an early-adopter market analysis for sub-Saharan Africa in order to begin the development of a global access plan.
- Successfully multiplexed malaria, HIV, and syphilis on the assay platform configured by Quansys. Started work on multiplexing iron and indicators of inflammation.
- Identified the US Army Medical Research Institute Unit: Kenya (Walter Reed, Kenya) as a potential partner to determine which iron biomarkers are appropriate to use in malaria endemic areas.
- Began assessment of other biomarkers used in ascertaining the etiology of anemia (i.e., hematological) that could be adapted to a POC format.
- Began proof-of-concept research and development work for a POC reticulocyte hemoglobin device.

Problems encountered and actions taken to resolve them

Members of the Human Hookworm Vaccine Initiative (HHVI) at George Washington University and Fundação Oswaldo Cruz (the Oswaldo Cruz Foundation) in Brazil have been approached as potential partners for determining diagnostic biomarkers for hookworm and schistosomiasis. As noted in earlier reports, these organizations were reluctant to work with us because they were not sure how they would benefit from such a partnership nor were they convinced that this idea was worthwhile. Chris Elias, the president of PATH, discussed the project with the head of the HHVI, Peter Hotez, to describe our

intentions and the nature of PATH's role in developing affordable diagnostics for resource-poor settings. Following this meeting, HHVI agreed to continue discussions with the project team. Our next step will be to engage in direct talks with them to describe our objectives so they can assess whether they would be willing to participate. We will hold on this step until we gather more information on the feasibility of a protein multiplexed platform and determine that this is the route that our project will take.

Lack of consensus of appropriate biomarkers for iron status continues to be a recurring issue. Despite our engagement with subject matter experts, we have come no closer to ascertaining if the biomarkers we are proposing are viable, and it is likely that the answer to this question may not be clear for several years. From a product development perspective, it is too risky to go forward with product development without knowing if the analytes we are proposing to measure are the correct ones for the product's intended use. Therefore, we were considering continuing with developing a test that combined hemoglobin and malaria alone (leaving off the iron biomarkers). Early on in the project, we identified reticulocyte hemoglobin as a potential biomarker that may not be affected by inflammation and therefore would be an appropriate biomarker to use in malaria-endemic areas. We determined that we should not proceed with this biomarker because the technology required to measure reticulocyte hemoglobin required sophisticated machinery that was not amenable to POC testing. We recently identified a product developer that designed a novel technology that could allow for this biomarker to be measured in a POC format. This information has breathed new life into the iron portion of our project, and we are now generating proof-of-concept data to determine feasibility of such an approach.

Despite early success multiplexing malaria, syphilis, and HIV on the Quansys platform, we found that one of the HIV control sera cross-reacts with other analytes. We are unsure whether this is an artifact of the Quansys multiplexing or whether the sample itself is from a co-infected patient. Additional HIV control serum is needed to ascertain whether the Quansys plates are valid. To rectify this, we are working with Quansys to determine where we can source additional HIV-positive control samples, how we can ensure they do not cross-react with malaria or syphilis, and how we can safely transport those samples to Quansys.

Next steps and milestones expected in the next six months

- Finalize the report of potential development partners and create a short list of three private-sector companies/academic groups that are capable of developing a multiplexed tool that meets desired product specifications. Approach the selected companies with our concept and determine their willingness to collaborate.
- Complete the validation of the multiplexed assay from Quansys with existing ELISAs and draft a final report on the performance of the assay.
- Continue proof-of-concept work for determining the feasibility of reticulocyte hemoglobin counting in a portable device.
- Send our bioengineer to the American Association of Clinical Chemistry's 42nd Annual Oak Ridge Conference: The Impact on Emerging Diagnostic Technologies, to look for additional companies capable of developing a product that meets our specifications.
- Generate data for determining proof of concept for reticulocyte hemoglobin.
- Draft a market analysis of early adopter markets and begin development of a global access plan.
- Draft a timing/efficiency analysis for nurses and patients in antenatal care clinics in a malaria-endemic area.
- Develop a partnership with Walter Reed, Kenya, for obtaining samples for validating research and development aspects of prototype development.
- Finalize the assessment of other biomarkers used in ascertaining the etiology of anemia—such as hematological—that could be adapted to a POC format.
- Refine product specifications where necessary to meet technological, budgetary, and timeline constraints.

- Generate a report on the percentage of hypochromic, reticulocyte count, and reticulocyte hemoglobin as indices for iron status.
- Complete a second iteration of the product specification sheet.
- Draft a product development plan to contain an assessment of reagent, specimen and equipment sources and availability; an estimate of the timeline and budget required for successful development; information on regulatory approvals required for the tool in relevant areas and their associated requirements; and potential funding sources for development activities.

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 to global introduction and market development for a CHX product.

Status of project as of March 2010

A draft introduction plan for the introduction of the CHX product in Bangladesh was developed and is being revised and strengthened based on operations research study results and input from stakeholders. Release of the introduction plan will occur once the dissemination meeting on the final CHX main trial results has been held, tentatively scheduled for July 2010.

Achievements and progress in the past six months

- Completed a draft CHX product introduction plan for Bangladesh and circulated it among collaboration partners to obtain feedback.
- Dr. Ziaul Islam, Associate Scientist at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR-B), initiated a demand assessment using the contingent valuation method.
- Completed formula optimization work with Frontage Laboratories, including compatibility and stability testing with the plastic primary container for the CHX product.
- Participated in the CHX main trial investigators meeting organized by Johns Hopkins University, January 25 and 26, 2010.
- Traveled to Dhaka in March 2010 to attend the fifteenth meeting of the Technical Review Committee (TRC) for the Projahnmo project in Dhaka where initial results of the CHX main trial were discussed. Also met with the CHX manufacturer and other collaborating partners (Research Training and Management International and ICDDR-B) during this time.

Problems encountered and actions taken to resolve them

The project timeline has been delayed due to inconclusiveness of CHX main trial results. We have modified the timeline to reflect the delay.

Next steps and milestones expected in the next six months

- Attend a regional dissemination of the CHX main trial results in Dhaka, tentatively scheduled for July 2010.
- Complete a demand assessment study, analyze data, and report final results to partners.
- Submit a revised work plan and timeline for the Bangladesh product introduction.
- Submit report of completed formula optimization work with Frontage Laboratories, including compatibility and stability testing with the plastic primary container for the CHX product.

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 March 2010

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 Biológico 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 an 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

- Conducted a rapid assessment of value exercise (RAVE) for gentamicin-Uniject. The results will be disseminated in an expert consultation in May or June.
- In collaboration with colleagues in Nepal, drafted the report of the Nepal field evaluation of gentamicin-Uniject. Findings from the report were disseminated in Nepal at a meeting in January 2010.
- Submitted an abstract to the Global Health Council 2010 annual meeting about the Nepal field evaluation of gentamicin-Uniject. This abstract was accepted and Jaganath Sharma will present the results on Tuesday, June 15, 2010, 10:45 am to 12:30 pm.
- Results from the gentamicin-Uniject study in Nepal were incorporated into a poster about the Nepal Morang Innovative Neonatal Intervention Program that was presented at the recent best practices meeting in Bangkok.
- Initiated planning for an expert consultative meeting to discuss current data on sepsis treatment and its application to the value proposition for gentamicin-Uniject.

Problems encountered and actions taken to resolve them

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

- Finalize and disseminate the findings from the gentamicin-Uniject field evaluation in Nepal.
- PATH staff will travel to Vancouver, British Columbia, Canada to present a poster about the results from the Nepal field evaluation of gentamicin-Uniject during the Pediatric Academic Societies' (PAS) Annual Meeting May 1–4, 2010.
- PATH will support travel of Jaganath Sharma from Nepal to present results from the field evaluation of gentamicin Uniject at the Global Health Council 2010 annual meeting in Washington, DC, in June.
- Submit a manuscript, in collaboration with BIOL, on compatibility/stability test results of the gentamicin-Uniject product for publication in a peer-reviewed journal.
- Submit at least one manuscript about the results from the gentamicin-Uniject field evaluation in Nepal for publication in a peer-reviewed journal.

¹ Uniject is a registered trademark of BD.

- Identify an appropriate site for a second field evaluation of gentamicin-Uniject as appropriate, 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 the rationale and justification for 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 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. 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 believe that an equivalent dose given by the ID route may achieve greater protection as determined by the standard measure of immunogenicity, the serum hemagglutination inhibition antibody titer one month following vaccination, as well as by an evaluation of the cellular (CD4+ and CD8+ T cells) response pre- and post-vaccination.

Status of project as of March 2010

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 Healthcare 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.

Achievements and progress in the past six months

- The manuscript from this study was e-published in *Clinical Infectious Diseases* on April 8, 2010. <http://www.ncbi.nlm.nih.gov/pubmed/20377407>.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- The researchers are examining cross-protection of ID vaccine administration against variant strains, including the H1N1 pandemic flu strain. This should be complete by the end of 2010.

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 March 2010

The focus of this project has shifted to meeting the objectives of the Global Development Alliance (GDA): Management of Birth Asphyxia; particularly to improve the availability of high-quality, affordable resuscitation devices and training materials in priority countries and to strengthen the supply chain logistics system for resuscitation devices (procurement, importation, storage, distribution/sale) in priority countries.

Achievements and progress in the past six months

- HealthTech became an implementing partner of the GDA for the Management of Birth Asphyxia. We will work to strengthen logistics systems and to create/increase demand for newborn resuscitation devices by working in close collaboration with Laerdal Medical AS (Laerdal).
- Attended various teleconferences related to terms of the GDA and work plan development.
- Hosted a visit from Tore Laerdal to discuss market development plans for low-cost resuscitation equipment.
- Created a schematic for overall market development for these products through the GDA including pathways for each implementing partner.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Per the GDA, HealthTech may conduct the following activities under the GDA memorandum of understanding with Laerdal:
 - Provide technical assistance to Laerdal to create global and country market development plans focused on increasing availability of high-quality, affordable resuscitators, training mannequins, and suction devices in low-resource settings.
 - Develop and implement a strategy for a sustainable distribution system for donated/at-cost goods.
 - Transfer knowledge and experience about potential market barriers to a fully functioning global distribution system.
 - Create and implement a strategy for how information about at-cost goods will be disseminated internationally.
 - Determine criteria for donated/at-cost goods.
 - Screen potential candidate countries for donated/at-cost goods.
 - Determine how to import/export product in the most cost-effective ways with a minimum of importation hurdles and duty.
 - Provide technical support to conduct initial in-house assessments of the new Laerdal suction device and then conduct field testing of this device in a low-resource setting.
 - Review training materials for the suction device for their suitability in low-resource settings and work collaboratively to make any modifications as needed.
 - Provide inputs to the American Academy of Pediatrics sustainability strategy for the Helping Babies Breathe training curriculum.

- Participate in the development of a monitoring and evaluation plan and identification of indicators; monitor and evaluate global distribution of devices; submit report as agreed by alliance members.
- Participate in semiannual alliance review and planning meetings.
- Disseminate the report from market research in the Economic Community of West African States when available.
- Prepare and submit a manuscript to an appropriate journal on the essential newborn care study in India, if possible.
- Disseminate a summary of results and recommendations from the market assessment in the South African development community (SADC) countries to key stakeholders as part of a policy brief (funded by another donor).
- Disseminate a SADC region-specific guide for 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 (PPH) 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 March 2010

Over the past six months, the Argentine pharmaceutical manufacturer Instituto Biológico Argentino (BIOL) has made progress improving commercial-scale production processes and increasing availability of the product through product registrations in Latin America. Product registrations have been obtained in two countries and are pending in seven others. An additional five registrations are planned to be filed in the second quarter of 2010. The World Health Organization (WHO) accepted BIOL's dossier for oxytocin in ampoules to begin the prequalification process; additionally WHO is planning to change the product specifications and encourage BIOL to submit its dossier for oxytocin-Uniject. Modest commercial sales of the product are underway in Argentina.

HealthTech is currently facilitating product supply for planned pilots and/or studies using oxytocin-Uniject in Ghana, India, Nicaragua, and South Africa (pending in-country approval of the study) in 2010. Additional potential pilot studies and/or product donation opportunities exist in the Dominican Republic and Honduras.

A second pharmaceutical manufacturer, Gland Pharma, received Indian regulatory approval in 2009. Additional stability studies are currently underway and are required for Gland Pharma to register the product in other countries; these studies are expected to be complete in the third quarter of 2010. Gland Pharma will produce oxytocin-Uniject for two planned studies in India—one to be conducted by the Indian Council on Medical Research (ICMR) and one by PATH's Oxytocin Initiative project, both are expected to be initiated in 2010.

HealthTech staff visited Indonesia to assess interest, conduct initial diligence with a potential third manufacturer of oxytocin-Uniject, and engage stakeholders in future pilot introduction activities in collaboration with USAID's Maternal and Child Health Integrated Program (MCHIP). A work plan is being developed for specific activities funded by the USAID Indonesia mission to integrate oxytocin-Uniject into the two-year maternal and child health bridging activities.

Achievements and progress in the past six months

- Completed a facility-level pilot introduction of oxytocin-Uniject in Guatemala in the fall of 2009 in close collaboration with the USAID-funded Prevention of Postpartum Hemorrhage Initiative (POPHI), the USAID mission, the Guatemala ministry of health (MOH), and other in-country stakeholders. Results will be disseminated at a stakeholders meeting conducted by the Guatemala MOH, including a discussion and evaluation of the prospects for potential national scale-up in that country.
- WHO accepted the dossier submitted by BIOL in June of 2009 for prequalification of 10-IU oxytocin in ampoules. PATH continues to provide technical assistance to BIOL to prepare for the WHO prequalification process, including that for oxytocin-Uniject.

¹ Uniject is a registered trademark of BD.

- BIOL has continued to drive forward registration in Latin America. In addition to registrations already obtained in Argentina and Guatemala, BIOL applied for product registration in seven other Latin American countries: Bolivia, the Dominican Republic, Honduras, Nicaragua, Paraguay, Peru, and Uruguay.
- Completed a preliminary market opportunity sizing study for BIOL's core Latin American markets.
- Worked with BIOL to develop a detailed plan to meet the supply needs for field activities over the next 12 months, including those planned for Ghana, Honduras, Nicaragua, and South Africa. BIOL produced a batch of 25,000 oxytocin-Uniject to supply planned or potential pilot introductions or studies in these countries.
- Worked with the PATH office in Nicaragua to plan for an introduction study of oxytocin-Uniject supported by the USAID mission.
- Attended the final Prevention of Postpartum Hemorrhage Initiative (POPPHI) meeting, Tackling the Biggest Maternal Killer: Progress and Challenges in Preventing Postpartum Hemorrhage, on November 20, 2009, in Washington, DC.
- Visited Gland Pharma in India to formalize plans for production in 2010 to support studies in India, discuss stability results, and provide technical assistance for Gland Pharma's oxytocin-Uniject product development effort.
- Gland Pharma completed a media fill and initial stability studies toward meeting international standards and began additional studies; results are expected in the third quarter of 2010.
- Made initial contact and began technical discussions with a potential pharmaceutical manufacturer of oxytocin-Uniject in Indonesia.

Problems encountered and actions taken to resolve them

Because the official WHO prequalification specifications called for "oxytocin in ampoules," WHO initially declined to accept BIOL's application for oxytocin-Uniject prequalification. However, at a recent meeting in Geneva with HealthTech staff, WHO stated they would change the specification and encourage BIOL to submit its dossier for oxytocin-Uniject. WHO prequalification, if achieved, will allow BIOL to offer its oxytocin-Uniject for procurement by United Nations agencies, in addition to elevating overall confidence in the product by potential public and private purchasers.

Gland Pharma has had an ongoing challenge of inconsistent operations of the Uniject device filling machine. Troubleshooting by PATH and BD India technical staff have identified the problem as an incorrect filling speed, and remedies have been suggested. Once Gland Pharma verifies that the machine is operating properly, they will move forward with production to support the ICMR and Oxytocin Initiative studies.

Next steps and milestones expected in the next six months

- Conduct a comprehensive Latin America market opportunity assessment to identify the best opportunities for early adoption of the product within the region, including prioritization of countries for introduction activities in Latin America, potential distribution channels, market analyses, and potential partners.
- Provide ongoing technical assistance to BIOL to prepare for WHO prequalification of oxytocin in ampoule and oxytocin-Uniject.
- Provide technical assistance to BIOL toward the optimization of broader commercial-scale production processes, including filling, inspecting, labeling, pouching, incorporating time temperature indicators, and final packaging.
- Assist BIOL in the evaluation, selection, procurement, installation, and testing of semi-automated pouching, printing, and labeling equipment (to be purchased by PATH and BIOL using non-HealthTech funding).

- Engage with BIOL to prepare public- and private-sector pricing strategies, based on refined cost models and improved production processes.
- Obtain new product registrations from the following additional Latin American countries: Bolivia, Costa Rica, the Dominican Republic, Ecuador, El Salvador, Honduras, Nicaragua, Panama, Paraguay, Peru, and Uruguay.
- Supply product for pilot introductions or studies in Ghana, Honduras, Nicaragua, India, and South Africa, as needed.
- Present a poster on the Guatemala pilot introduction study at the 1st Latin American and Caribbean Conference on Global Health, held in Cuernavaca Mexico, April 9 to 11, 2010.
- Disseminate the results from the 2009 Guatemala pilot at a stakeholders meeting conducted by the Guatemala Ministry of Health, including a discussion and evaluation of the prospects for potential national scale-up in that country.
- Maintain and update existing tools for countries and programs planning the introduction of oxytocin-Uniject. These tools include technical overview documents, pilot planning guides, training materials, and advocacy resources.
- Continue the dissemination of the oxytocin-Uniject introduction tool kit to the global health community including countries and maternal and child health programs introducing efforts to reduce PPH. The tool kit is available via the internet and as a CD-ROM.

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 March 2010

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 and resulted in encouraging data that suggested moving forward with commercial-grade reagents. HealthTech has secured these key reagents from commercial partners for research and development purposes after extended intellectual property negotiations. Research and development of the test has been reinitiated.

Achievements and progress in the past six months

- Completed agreements with collaborators to gain access to the reagents necessary for the research and development of the test.
- Reinitiated research and development of the test.

Problems encountered and actions taken to resolve them

A slow response from collaborators to secure agreements and provide critical reagents has hampered the ability to perform laboratory-based research. However, the agreements are now in place and reagents are available for the development of the test.

Based on the availability and the highly purified nature of the reagents, we have started development of a modified test that could be more sensitive and specific. Early in the research and development process, this approach has indicated technical hurdles (such as reproducibility and stability) that must be addressed. If we are unable to overcome these hurdles, research and development efforts will revert to the previous test format.

Next steps and milestones expected in the next six months

- Continue research and development using 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 March 2010

The RBP-EIA immunoassay remains commercially available through Scimedx, although because of limited demand and therefore commercial imperatives, manufacturing has moved from off-the-shelf availability to custom production of the conjugate with an 8- to 10-week delivery time from placement of order. The reversal of this manufacturing process will occur when volume reaches a critical demand. Utility and application in the field continue to be reinforced, but the politics of uptake by major players remains the over-arching issue.

Achievements and progress in the past six months

- There has been one order (230 units) during the past six months for the RBP-EIA test kit.
- The World Health Organization has announced the establishment of a committee to address biomarker indicators for both population-based surveys as well as for diagnostic application. Results are due in December 2010.

Problems encountered and actions taken to resolve them

The problem is not science, it is the politics of uptake. PATH will continue to work with USAID and within the international community to support and participate in the development of biomarker standards in order that uptake and implementation can then become the focus.

Next steps and milestones expected in the next six months

- Three additional third-party population-based surveys are scheduled by Macro International Inc. Demographic and Health Surveys, for the second half of 2010 that will use the RBP-EIA assay kit and thus continue to qualify its field validation.
- HealthTech will provide continued technical support to Scimedx, as requested, and continued commercial due diligence of the company will remain a priority.

Systematic architected rational approach to planning, managing, and acquiring software products in global health

Goal of project

The goal of this project is to develop, document, and validate approaches and practices that advance a more systematic, architected, and rational approach (SARA) to the design and development of health information systems in resource-constrained settings.

HealthTech has begun to elaborate a set of practices, guides and templates that move health management information system projects toward SARA. Thus far, this work has focused on the design phase of projects with a heavy emphasis on user and system requirements. A new set of activities will build on this beginning to include the other phases of planning, creating, acquiring, and deploying health management information systems and software products in global health. These activities build on our growing experience in applying the SARA framework across projects and throughout the project lifecycle from planning to deployment.

These activities will include:

- Developing guidelines for countries and country support teams to consider when acquiring information and communication technology including software products.
- Identifying minimum criteria and competence that developers of software products should be able to demonstrate.
- Developing guidelines on how to assess existing products and information systems against user and system requirements.
- Developing guidelines for countries and country support teams to consider when planning and designing health management information systems and specific software applications.

Status of project as of March 2010

This effort has advanced to the documentation and validation stage in four discrete areas, each exploring some common and unique aspects of SARA. First, HealthTech continues to develop the Cold Chain Equipment Manager (CCEM) software product, adapting existing industry practices and open source tools for the management of source code and the development process. We have implemented an open source server platform enabling developers from around the world testing CCEM to access a common repository for logging and tracking software bugs and issues. Secondly, we are moving from functional requirements to software development in Tanzania with a developer who is working under a subcontract to PATH. This will validate the completeness of the functional requirements collected through SARA. Thirdly, we are validating SARA requirements for a solution that combines hardware and software engineering in the Smart Connect project—a project that involves building a device that allows basic data connectivity between a rural health post and the internet. Finally, we are applying SARA to the documentation of system requirements in Tanzania that will support the mobile solution being developed above. This will also leverage the methods and tools being developed in the other three activities based on the documented requirements.

Achievements and progress in the past six months

- Developed a product development structure for CCEM.
- Implemented the Bugzilla server and software environment for CCEM, allowing global access.
- Applied SARA and produced functional requirements in Tanzania for scoping and contracting software development.
- Reviewed and disseminated SARA and accompanying methodology to our collaborators, the International Organization for Standardization Technical Committee 215 Joint Work Group, at a meeting in Bellagio, Italy.

Problems encountered and actions taken to resolve them

Migrating the CCEM product development effort using SARA has uncovered areas of high-level scope that when described in detail identified gaps in the documentation of functional requirements. This was addressed by assigning a two-person technical team—one as the subject matter expert and one to serve as business analyst to elaborate and document requirements. This has been very effective and efficient to address the gaps in requirements.

Next steps and milestones expected in the next six months

Use SARA to document:

- CCEM beta testing and product release activity.
- CCEM transition planning for sustainable support and maintenance.
- The delivery and evaluation of the Tanzania community health worker solution.
- The Phase 1 development of the Smart Connect prototype.

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 will focus on:

- Improving the ability of immunization program managers to monitor vaccine distribution systems, vaccine stock, and equipment allocation to ensure appropriate cold chain capacity and vaccine safety through improved cold chain management information systems (MIS).
- Working with private-sector and other partners to investigate promising refrigeration technologies such as the Twinbird Stirling cooler refrigerator. Due to a funding obligation decrease during the current term, there will be no significant HealthTech resources allocated to identify, develop, evaluate, or introduce alternative technologies for refrigeration and other cold chain functions, however the team will continue to monitor promising cold chain technologies.

Status of project as of March 2010

The immunization delivery technologies project team has been active across two focus areas—cold chain MIS and cold chain technologies. The project team has been shifting priorities over the past year to focus mostly on the cold chain MIS area, with limited resources going towards the cold chain technologies area. This report will identify a number of accomplishments that were met during this reporting period.

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) Version 2.1 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

- Contracted the services of a Seattle-based software development firm in August to complete the necessary workflow changes, systematic code updating and management, end-to-end testing, and user interface improvements to deliver a validated version of a cold chain equipment manager (CCEM) software tool developed with Microsoft Access 2007. The final product—CCEM Version 2.1—was delivered on December 2, 2009.
- Completed thorough in-house user acceptance testing of CCEM Version 2.1.
- Contracted the services of a software development consultant to make minor revisions to CCEM 2.1.
- Adopted software industry practices for managing, tracking, and classifying bugs and other issues using a standard tool, Bugzilla.
- Completed detailed process flow documentation of CCEM implementation for multiyear cold chain equipment planning.
- Developed a long-term product management plan for CCEM, including a strategy to move to a web-based platform for Version 3.0 in 2011.
- Updated and finalized a CCEM Version 2.1 user manual.
- Responded to a solicited scope of work request from UNICEF to use CCEM to assist with rebuilding the cold chain in Haiti. Proposed project activities would begin in mid-2010.
- Presented the concept of a CCEM 3.0 web-based platform to Hewlett Packard to start conversations around opportunities for future collaboration.

Cold chain technologies

- Developed a work plan, timeline, and budget to complete two objectives of the SolarChill consortium. Objective 1 is to define the local and regional market size and value for SolarChill refrigerators; evaluate SolarChill refrigerators in the field, including overall performance, maintenance requirements, problems, and acceptability; and create a commercialization plan for a regional manufacturer. Objective 2 is to transfer the SolarChill technology to capable and interested companies in Colombia and Africa and collaboratively develop and implement a sustainable commercialization strategy that meets the local and regional demand.

Problems encountered and actions taken to resolve them

Cold chain MIS

After receiving the revised version of the software from the developer, the CCEM team faced the challenge of making sure that the program was able to support the entire cold chain planning process in a robust manner. To address this concern, we developed a detailed process flow diagram and worked it through with a cold chain expert, documenting all issues identified. The identified issues are now being addressed in a managed fashion, working with a software development consultant.

In order to deploy CCEM, it will be necessary to have the data from a national cold chain inventory. The initial field deployment of CCEM has been delayed because of difficulties in identifying a country with either available inventory data or the necessary funds to conduct a new inventory. Plans to introduce CCEM to stakeholders in Kenya in December 2009 and collect data in early 2010 were delayed due to an administrative reorganization of districts in Kenya. Team members will be visiting Tanzania to investigate various mechanisms for developing an inventory, including exploring options that would be less costly than conducting comprehensive facility visits.

Next steps and milestones expected in the next six months

Cold chain MIS

- Travel to Tanzania in April 2010 to meet with WHO and Tanzania Ministry of Health staff to plan and budget for the introduction of CCEM in Tanzania in late 2010.
- Train data collection teams and complete a national cold chain inventory in Tanzania using CCEM.
- As funding allows, conduct a three-day workshop in Seattle to train key consultants and select country representatives on the use of CCEM to properly conduct a cold chain inventory and multiyear cold chain equipment plan.
- Develop CCEM training materials including quick start guide(s) and short video tutorial(s).
- Release CCEM 2.1 for public use by posting it (along with associated user documentation) on the PATH website.

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, which included over 140 individuals from 11 countries. 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 March 2010

HealthTech is helping to coordinate follow-up activities from the symposium. These include developing an advocacy brief that makes the case for future development and support of multipurpose prevention technologies, a brochure to accompany the longer case document, and an outreach plan for distributing the document after it is printed.

Achievements and progress in the past six months

- Drafted an advocacy brief.
- Coordinated three rounds of review and editing, including external review by 18 stakeholders/representatives from key organizations.
- Designed graphics and layout for the advocacy brief.
- Designed a one-page companion piece brochure to accompany the advocacy brief that is currently in production by the PATH graphics team.

Problems encountered and actions taken to resolve them

The original budget for the advocacy brief projected a streamlined schedule for drafting the document, conducting one round of outside review with the core advisory team and outside experts, and then moving quickly to production. The original goal was to have the document available by February 2010 to begin raising awareness about this new initiative. After discussions with the core advisory team in December and January, we realized that it was important to include additional rounds of review to ensure that the advisory team agreed with final revisions before sending the document to layout. As part of the fiscal year 2010 HealthTech budget request, we submitted a request for supplemental funding to cover the unanticipated expense associated with additional rounds of review. The advocacy brief and an associated set of talking points (brochure) are now scheduled to be available for launch at the Microbicides 2010 conference in May.

Next steps and milestones expected in the next six months

- Complete the layout and design of the advocacy brief and companion brochure and get approval from the core advisory group on the final design layout. Print documents and ship them to the Microbicides 2010 conference.
- Disseminate documents at the Microbicides 2010 conference by HealthTech staff, and other members of the advisory group, as well as through other relevant meetings.
- Post advocacy brief and companion brochure documents on California Microbicide Initiative's, PATH's, and other initiative partner's websites.

- Develop an outreach strategy that includes the briefing document and other project resources enabling their use by a broader coalition of stakeholders in discussions with researchers, product developers, policymakers, funding agencies, and reproductive health program advocates.

Microbicides delivery systems

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 March 2010

HealthTech has completed initial feasibility research on the PATH Woman's Condom with UC-781-loaded microbicide film and is advancing research and development activities to show proof of concept of the SILCS Diaphragm as a controlled-release microbicide delivery device. HealthTech will soon initiate a comparative safety study of a prefilled applicator and user-filled applicator using Tenofovir gel and is in the early planning stages of a feasibility study of the controlled-release SILCS Diaphragm to assess performance, acceptability, and safety (with the California Family Health Council [CFHC]).

Achievements and progress in the past six months

- Received conditional approval by the PATH, Profamilia, and Dominican Republic National research ethics committees for the protocol for a comparative applicator safety study with Tenofovir 1 percent gel, to be conducted with Profamilia in the Dominican Republic. We are currently responding to a final set of contingency questions for the PATH institutional review board (IRB).
- Completed testing for quality assurance of Tekpak user-filled applicators at PATH.
- CONRAD conducted biocompatibility testing of the Tekpak applicators. They have also completed manufacture and packaging of Tenofovir 1 percent gel for the study.
- PATH and CONRAD are finalizing clinical material agreements, a monitoring agreement, and the transfer of sponsor obligations.
- In collaboration with Queens University of Belfast (QUB), continued development and testing of the SILCS Diaphragm as a controlled-release device and determined that UC-781 was incompatible with the manufacturing processes of the SILCS device.
- Received agreement from Medivir to provide 100 g of MIV-160 for the manufacture of prototypes and in vitro testing.
- Received approval from USAID for the purchase of injection-molding equipment for installation at Queens University of Belfast for rapid prototyping and preparation for the manufacture of drug-loaded SILCS devices with progesterone and MIV-160 to validate the feasibility of a controlled-release SILCS device.
- Completed proof-of-concept studies in collaboration with the University of Pittsburgh, Magee-Womens Research Institute Pharmaceuticals Group, and CONRAD that illustrate the feasibility of anti-HIV drug incorporation into the PATH Woman's Condom capsule. These studies specifically demonstrated that UC-781 can be formulated into the condom capsule. Two prototype UC-781-containing capsule formulations were developed and tested. Placebo formulations were compared against the currently used capsule.

Problems encountered and actions taken to resolve them

It was determined that UC-781 was incompatible with the manufacturing processes of the SILCS controlled-release device. HealthTech and QUB initiated discussions with other microbicide sponsors to explore or secure access to additional microbicide candidates for evaluation in the SILCS Diaphragm, including: MC1220 (non-nucleoside reverse transcriptase inhibitor [NNRTI], University of Cagliari, Italy); MIV-160 and MIV-170 (NNRTI, Medivir); darunavir (protease inhibitor, Tibotec-Virco); nevirapine (NNRTI, Boehringer Ingelheim). As a result of discussions with Medivir, we have received approval for access to 100 g of MIV-160 for future nonclinical research. This is an important development that will enable us to advance product testing with a relevant NNRTI microbicide candidate.

Due to delays in the purchase of the injection-molding equipment to be installed at the Medical Polymer Research Institute at QUB (a facility jointly supported by the Schools of Pharmacy and Mechanical Engineering), this equipment has not yet been installed as planned. With recent USAID approval, the purchase and installation will now move forward.

Next steps and milestones expected in the next six months

- Initiate a comparative applicator safety study with Profamilia, including the receipt of final IRB approvals, submission by CONRAD of an investigational new drug amendment to the US Food and Drug Administration, delivery of the product to the study site, completion of a study manual, a site initiation visit, and initial enrollment.
- Install and optimize precision liquid injection-molding machinery at QUB, and develop and optimize appropriate manufacturing methods to provide various test batches of MIV-160 and progesterone-loaded SILCS Diaphragms for more rapid design iteration and testing.
- Commission several new molds from a QUB machine shop. These molds will be suitable for spring production and will greatly increase the capability of QUB pharmacy engineers to undertake material assessments, conduct in vitro and mechanical testing with MIV-160-loaded devices to assess delivery, and determine appropriate prototype variations to include in a clinical study with CFHC.
- Establish an agreement with CFHC 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 project 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 March 2010

Shanghai Dahua Medical Apparatus Co. (Dahua), the current manufacturer of the WC, has worked on advancing the production processes and with HealthTech and local research partners on implementing a couples' use study. Results from this study, which we expect to be completed by late 2010, will be submitted to the China regulatory authority. Our current plan for approval by the Chinese State Food and Drug Administration (SFDA) remains unchanged, with market clearance expected 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

- Attended a Universal Access to the Female Condom Joint Programme (UAFC) joint platform meeting in Amsterdam in October and convened a global-level strategic advisory group to advise on WC launch and global introduction strategies.
- Used funding from a third party to support Dahua's purchase of new equipment for scaling up the lubricant and dissolving cap production. The equipment was installed and verified by the third-party donor.
- Completed final sourcing of raw materials, and the first products from the Dahua assembly line became available. HealthTech performed bench tests in Seattle and confirmed the quality of the product.
- Product quality was positively verified by testing at Family Health International (FHI) in North Carolina.
- Validated production at Dahua through visits by HealthTech staff and a condom production consultant.
- Hired a regulatory consultant to advise on appropriate pathways for the WC product, including the International Organization for Standardization and the United States Food and Drug Administration (USFDA).
- Prepared a technical dossier of production and quality assurance/quality control testing for the Woman's Condom and submitted this to CONRAD for the investigational device exemption (IDE) application to the USFDA.
- Dahua produced and shipped a complete inventory for the CONRAD Vaginal Semen Exposure and Clinical Failure study.
- HealthTech researchers traveled to Shanghai in early March to review the couples' use study protocol with the in-country research teams 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. Began data collection at two sites in the Shanghai area.
- Reviewed a draft report of focus group discussion research among nine potential user groups in the Shanghai area.
- Completed the market evaluation and segmentation study; results will be used to inform the product launch plan (tentatively scheduled for early 2011).

- Hired a Chinese consultant to draft a public-sector product introduction plan.

Problems encountered and actions taken to resolve them

Production scale-up and increased efficiency is what is needed to drive the cost of the product down. In order to achieve cost efficiencies, Dahua will need to invest in equipment for scaled-up production processes. They are currently seeking funding to support the following scale-up options (1) ring welder, (2) lubricant packaging machine, (3) pouch stuffer (they have available labor to stuff pouches so automation is not so critical), and (4) in-house film production. The anticipated cost of the ring welding machine is about US\$30K. The investment needed for film production machinery will be about US\$800,000. PATH is assisting Dahua to identify and secure funding for this equipment.

HealthTech is closely monitoring any potential changes in product specifications due to the manufacturing scale-up processes noted above. Ideally, any product that is manufactured using scaled-up processes will remain within current product specifications.

Next steps and milestones expected in the next six months

- Finalize the focus group discussion study results and prepare a final report and manuscript, if appropriate.
- Finalize the report on the China public-sector product introduction plan and use the results to inform a product launch plan.
- Finalize a China market development plan that uses a total market approach of combining public and private sectors.
- Define a product launch plan for the China market.
- Complete data collection for the couples' use study and prepare failure mode data for submission to the SFDA. Draft the final report and manuscripts for performance and acceptability, as time permits.
- Conduct study monitoring visits by Reproductive Health and HIV Research Unit researchers at the beginning and end of the couples' study.
- Dahua will install the scaled-up pouch welding equipment that has capacity to produce up to 10 million units annually.
- Interview and select two MBA interns for summer placements at Dahua (these positions are not funded by HealthTech) to work on China market generation and product branding activities. Provide mentoring and oversight of each intern and coordinate dissemination about their experiences at the end of their placements.
- Participate with CONRAD and the National Institutes of Health in meetings with the USFDA regarding the IDE application needed for the contraceptive effectiveness study.
- Dahua will produce and deliver a complete inventory for the China clinical study as well as for the National Institute of Child Health and Human Development Contraceptive Clinical Trials Network contraceptive effectiveness study in the United States.
- Draft a report on the global market development plan and use the results to inform the revision of the WC global business plan.
- Participate in meetings convened by UAFC in New York City and/or Washington DC.

SILCS Diaphragm microbicide delivery system assessed through MRI

Goal of project

This study was designed 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 assessed 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 taken before and after simulated intercourse and after six hours of product wear assessed gel dispersion and retention over time. Women reported on the acceptability of the different gel delivery systems via microbicide delivery system acceptability scales. The candidate microbicide BufferGel[®], manufactured by ReProtect, was used in this study.¹

Status of project as of March 2010

Our previous report noted that a final study amendment was developed to allow the University of Pennsylvania (U Penn) researchers to conduct a final round of MRI scans with a subset of the study participants. This last round of MRI scans was needed to help interpret the scanned images from the main portion of the study that had been completed in June 2009. The amendment was approved by the PATH Research Ethics Committee and the U Penn institutional review board (IRB), and the approvals were reconciled by December 2009. U Penn contacted three of the six women who participated in the study and scheduled return visits for a final sequence of MRI scans, which were conducted between December 2009 and March 2010.

Dr. Kate Morrow (from Lifespan/Brown University) compiled results from the qualitative portion of the study and sent this for HealthTech review. The research team (HealthTech, Dr. Morrow, and U Penn researchers) is scheduled to meet in late April to review the findings from the qualitative analysis and the imaging portion of the study and assess the correlation between coverage provided by different gel application scenarios and women's perception of acceptability and ease of use with the different gel scenarios.

Achievements and progress in the past six months

- Received approval of the study protocol amendment for the final round of MRI scans by both PATH's research ethics committee and by the U Penn IRB and the approvals were reconciled. U Penn successfully implemented the Part 3 MRI scans from December to March.
- Dr. Kate Morrow compiled qualitative results from the acceptability questionnaires and the in-depth interviews.
- Extended the subagreements with U Penn and LifeSpan (no cost extensions) to allow time to complete the final MRI scans and for the research team to meet and compile the final report.

Problems encountered and actions taken to resolve them

The final stage of this study took longer than anticipated for the following two reasons: (1) delay in receiving approvals from the U Penn and PATH ethical review committees and (2) difficulty scheduling final MRI scans due to protocol requirements (i.e., needing to sequence the scans at specific times in the women's menstrual cycle if she was not already taking oral contraceptive pills) and scheduling around the end of year holidays. The research team worked diligently to complete this study as quickly as possible.

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

- The research team will meet at U Penn in late April 2010 to review findings from both qualitative and MRI portions of the study.
- The research team will draft the final study report and decide on steps regarding the dissemination of findings.

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 evaluated two scenarios with gel delivered by the SILCS Diaphragm, and compared 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 March 2010

California Family Health Council (CFHC) successfully completed the clinical portion of the study in December 2009. CFHC collected data from 34 couples who each completed multiple uses of three gel delivery scenarios. All three scenarios received favorable ratings from both genders for ease of application, acceptability, and perceived effectiveness. There were no statistically significant differences in terms of acceptability between the SILCS Diaphragm with gel on one side (5 ml) compared to the SILCS Diaphragm with gel on both sides (8 ml).¹ On the other hand, both female and male participants tended to rate the applicator-alone scenario significantly more favorable than either the SILCS Diaphragm gel delivery scenario for all attributes, except for messiness/leakage and effectiveness. While disappointing on the one hand that couples preferred the ease of the vaginal applicator, this finding does seem to support our initial supposition that use of the SILCS Diaphragm may help hold the gel in the vagina and reduce messiness/leakage. Since this study population was not at risk of pregnancy or sexually transmitted infections (STIs) (due to study protocol eligibility), it raises questions how results might have differed if the study population perceived themselves to be at risk of STIs or pregnancy.

The qualitative results from the focus group discussion at the end of this study provided insights into how women in the United States would like to receive information about the SILCS Diaphragm (through a doctor's office and through women's magazines), as well as points that appeal to them about the SILCS Diaphragm (*hormone free and hypoallergenic; different than the beige dinosaur—the Ortho Diaphragm*), and packaging (compared the case to the size of a smart phone; liked that it can be concealed easily; want a gel package that fits in the case so is easily transported).

CFHC drafted study findings, and a final report is being reviewed by PATH. Results from this study have been shared with the researchers from the University of Pennsylvania (U Penn) MRI study since the two studies each evaluated the same gel-use scenarios. HealthTech recently extended the CFHC sub-agreement to the end of May to allow time for reviewing and completing the final report.

Achievements and progress in the past six months

- Recruited a total of 36 couples for this study; 34 couples completed all study procedures.
- Conducted a focus group with a subset of the female participants in December to assess study findings and investigate use patterns and acceptability.
- CFHC drafted the study report and it is being reviewed by PATH.
- PATH provided a no-cost extension of the CFHC sub-agreement to allow time for data review and report writing.

¹ For ease of application and using BufferGel[®] packaging options available, women use a prefilled applicator to apply the 5 ml of gel to the cervical cup and split the dose of an 8-ml sachet when applying gel to the cervical and vaginal sides of the SILCS Diaphragm cup.

Problems encountered and actions taken to resolve them

An unexpected finding from this study is that women had a high degree of dissatisfaction with BufferGel[®], the gel product used in the study. This may have influenced how the women perceived use of the SILCS Diaphragm with gel scenarios. We will look at these results in relation to results from the U Penn study as well.

Another challenge in interpreting these study findings is that protocol eligibility required women in this study to be protected from pregnancy and at low risk of STIs. This raises the question about how study results might have differed if the study population perceived themselves at risk.

Next steps and milestones expected in the next six months

- Complete study report and determine next steps for disseminating study results.

Skunkworks

Diagnosics

Development of a recombinase polymerase amplification assay for pulmonary tuberculosis

We have initiated a new project to develop a tuberculosis (TB) molecular diagnostic assay. There is an urgent need for a rapid molecular diagnostic assay to detect pulmonary TB, especially in regions severely affected by the HIV epidemic. In a separate project, PATH scientists have been collaborating with TwistDx (a Cambridge, England-based company that has developed recombinase polymerase amplification [RPA]) to develop an infant HIV assay. RPA has shown great potential to be a rapid and sensitive DNA amplification tool, especially for diagnostic assays in resource-limited settings. Therefore, we are now proceeding to develop an RPA TB assay. The project is in the early design stage in which TB genomic sequences and the pertinent literature are being searched for effective target regions for a potent RPA TB assay. A preliminary report has been drafted which identifies and analyzes DNA target sequences from 35 independently developed TB diagnostic assays. The target DNA sequences from these assays were compiled, aligned, and compared to the TB DNA genome. The report is designed to identify the ideal target with which to base an RPA TB assay based on the performance of these published assays. TwistDx, with their experience in RPA assay design, is developing the primers and probes sequences based on information from this report. The Washington State TB Reference Laboratory has agreed to participate in this project and has supplied mycobacterial DNAs for the assay development at TwistDx. Once a prototype assay is designed, it will be evaluated on TB DNA samples at the TB Reference Laboratory and at PATH.

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.

Sales of the *Chlamydia trachomatis* antibodies we used in our first generation system were discontinued by the manufacturer (Dako Inc.). This required that we conduct a comprehensive literature search for new antibody candidates. We carried out a lab-based evaluation of the new candidates' utility for our system and through this process we selected a new set of antibodies. We have since resumed evaluation of antibody conjugation, wash buffers, sample preparation, and antigen lysis resulting in an early prototype device for use in developing the strip reader. Our previous commercial partner (Axxin Inc.) has decided not to pursue the development of the wave guide reader. This resulted in intellectual property reverting back to our initial development partner (Fluidyx Inc.) which now operates under a new trade name (Floria Biosystems.) Floria Biosystems has secured additional Australian government funding to further develop and simplify the reader. Their business plan includes using this reader in applications for low-resource settings (chlamydia) and developed-country settings (influenza A). Floria will deliver a functional reader, updated software, and technical service—all of which is needed for the continued development of the chlamydia assay. Additionally, Floria will continue research on locating and evaluating miniaturized components for an eventual handheld device. HealthTech will evaluate the underlying technologies for the handheld device against commercially available benchtop analyzers and continue research and development of the strip, specifically technologies for immobilizing and rehydrating conjugated europium beads in the lateral flow test strip.

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.

During the current reporting period, we focused on identifying antacid candidates for use in conjunction with orally dosed tablets. For this purpose, commercial over-the-counter antacids, as well as the ones used along with oral vaccines, were screened for their compatibility with ACE enterotoxigenic *escherichia coli* (ETEC) vaccine strains and for their stomach-acid neutralization capacity. The rice syrup solid-based antacid buffer, Ceravacx, was the best candidate, both in terms of offering stability (2h, 37°C) to the three vaccine strains as well as for neutralizing the stomach acid and maintaining the pH in a stable range of ~4 (2h, 37°C) post neutralization. Our ongoing work involves manufacturing of placebo tablets in Ceravacx buffer with various binders at Oregon Freeze Dry. Our next step involves the evaluation of dissolution characteristics of the tablet and the compatibility of tablet excipients with ETEC vaccine strains. The production of an ETEC vaccine tablet is anticipated in April, and the stability data of the ETEC vaccine in tablet formulation will be available by July 2010.

Hybrid vaccine refrigerator

HealthTech has joined with industry partner Global Cooling (GC) to focus on the application of the Stirling cycle compressor and battery-free solar direct drive to vaccine refrigeration. GC has made significant innovations in Free Piston Stirling Coolers (FPSC). Compared to a typical vapor compression cycle, the Stirling cycle compressors require lower starting power and have been reported to operate more efficiently with solar direct drive operation. PATH developed an innovation that combines engineered phase change material (EPCM) and vacuum panels that significantly increase the hold-over time for these coolers for off-grid use while lowering the overall energy demand when power is available. We are in the process of developing a prototype that combines GC and PATH innovations and have been testing performance of early configurations. It is expected that working prototypes of the battery-free solar powered refrigerators will be deployed toward the end of the next six month period. They will be tested in the field and submitted for World Health Organization (WHO) performance, safety quality (PQS) testing if their performance is proven in the field. Finally, we enlisted the assistance of a local market research team, Last Mile, to assess the value proposition of FPSCs.

HealthTech skunkworks funds have been leveraged to apply EPCM latent heat storage and the high thermal resistance of vacuum-panel insulation to passive coolers for vaccine transport and storage at outreach facilities. Prototypes have been tested, and we have evidence this technology will pass the WHO PQS testing as well as the Optimize Passive Cooler Challenge. We are currently seeking funds to finalize development and submit a prototype for third-party testing to these standards.

Insulating carrier for reconstituted vaccine vials

We propose to develop a prototype insulating carrier for individual 5- and 10-ml vaccine vials used for reconstitution. Reconstituted vaccines must be kept below 10° C, for 6 hours. The goal is to achieve this at an ambient temperature of 32° C. At this point, cost constraints and volumetric limits have not been well defined, but we will make a prototype to understand how long a given size container would keep the

vaccine below 10° C. If the first prototype produces a promising result, more effort can be made to optimize the design and determine appropriate specifications for a viable product.

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.

During this reporting period we optimized the thermosensitive gel (TRG) formulations and selected the most applicable seven formulations for in vitro and in vivo screening studies. All of these formulations were tested for gelation in human saliva (in vitro) as well as for gelation at 37°C in various other testing applications including mucin/agar plates, angled petrie dishes, and various volume gelation. The seven thermosensitive formulations were tested for TRG-mediated stain retention and for in vitro cytotoxicity of TRG at Walter Reed Army Institute of Research (WRAIR). All formulations were also tested for LDH release as a means of determining cytotoxicity. The in vitro data demonstrated low cytotoxicity for four formulations based on LDH release and microscopic assay. Our next steps include in vivo evaluation of gelation and spreadability in guinea pigs and mice at the University of Washington followed by an immunogenicity study using two selected formulations in mice. In addition, the antigen uptake of all formulations will also be tested to determine the formulation that has good retention and release of the antigen at WRAIR. We anticipate having immunogenicity data with a *Shigella* vaccine and a tetanus toxoid (a model antigen) for sublingual immunization by July 2010.

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 the 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 engaged key stakeholders, such as Dr. Mendis with the World Health Organization (WHO) who is the 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. We drafted a scope of work and plan to submit a proposal to other donors in May 2010.

Evaluation of biomarkers for neonatal sepsis

Within the first 28 days of life an estimated 3.7 million babies die annually, and when perinatal deaths are included, which groups stillbirths with early neonatal deaths, it is estimated the total is 5.9 million deaths annually. Infections are implicated in as much as 36 percent of neonatal deaths. To date, no diagnostic tools exist that empower clinicians to promptly determine the infection status and severity of infection

among neonatal patients. Development of such a tool would improve neonatal health dramatically, especially in low-resource settings where the majority of the global mortality burden is centered.

Proteogenix Inc. (Costa Mesa, CA) has identified a set of biomarkers which appear to strongly predict outcomes in neonates with infections in US-based populations. However, these biomarkers have not been evaluated in the developing world. PATH, Proteogenix, the University of Washington, and the Bill & Melinda Gates Foundation are investigating the feasibility of adapting this set of biomarkers to a simple field-friendly screening test that could be used in high-burden low-resource settings. In parallel, we will be working with investigators from the International Centre for Diarrhoeal Disease Research, Bangladesh, and Dhaka Shishu Pediatric Hospital, Bangladesh, to collect a preliminary panel of specimens from infected and uninfected neonates to challenge the performance of these biomarkers in predicting poor outcomes. These activities will inform our decision to proceed with further development of a rapid diagnostic test and larger population-based evaluation studies.

Haemostatic agents for postpartum hemorrhage prevention

Postpartum hemorrhage (PPH) is the leading cause of maternal death in low-resource settings. We have researched and advanced innovations for the control of PPH and patient stabilization for transport to obstetric surgery. These innovations include oxytocin delivery, the non-pneumatic antishock garment (NASG), and the balloon tamponade. We are now expanding our research to include intrauterine haemostatic agents.

There are multiple validated haemostatic products for use to control external bleeding yet only anecdotal reports of PPH-related intrauterine use. We are currently evaluating both recombinant and Kaolin-based products for cost, form factor, and usability. We believe an easy to administer format such as thermo-gel, absorbable gelatin sponge, or a spray or foaming gel, may enable semi-skilled birth attendants to administer a single, life-saving dose of the haemostatic agent to the uterus through the cervix at the first signs of PPH. We identified a stage-gated scope of work to demonstrate proof-of-principle and are currently seeking funding for these activities. These activities include:

- Identification of specific indications a haemostatic product might be useful for (cervical lacerations, uterine atony, or both).
- Identification of scenarios for use—what level of the health care system might benefit most?
- Develop a stakeholder-centered draft product specification.
- Gather stakeholder input on concerns, contraindications, and other constraints around, for example uterine packing, that might help influence both design and application.
- Develop and prototype up to three PPH-appropriate configurations we can take into the field to facilitate (nonclinical) evaluations and focus groups for the purpose of refining the specification and scenarios for use.

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 are assessing 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. Our consultant from Johns Hopkins University is currently finishing up his scope of work and we expect to have a draft report by the end of April.

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

Creating a package of underused 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 PremiePackage of interventions, both bundled into one tool bag and as stand-alone interventions. To date, the team has used 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). Clinical care algorithms have been developed for maternal (preterm labor and delivery) and newborn (immediate) care. These algorithms are the basis of an essential capacity/quality assurance component of a larger package of interventions under the title Perinatal Intervention Program. A concept paper is being produced that provides a broad overview of this programmatic approach. Identification of essential equipment required for specific levels of care is underway. Optimal operational pathways for low-resource settings still need to be determined. Testing the acceptability and feasibility of the PremiePackage interventions in a mid-level resource setting will be critical to demonstrate the usefulness of this approach. In the future, a more detailed paper that describes current best practices, gaps in practice, and commercial availability of equipment for each specific intervention may be produced.

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 include aggregating and documenting the outputs of the requirements-gathering process.