HealthTech IV

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Semiannual Report
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Highlights and milestones of HealthTech projects during the past six months

- The introduction of depo-subQ provera 104™ injectable contraceptive in the Uniject™ prefilled injection system (depo-Uniject™) team prepared and delivered background information for USAID concerning the global market for injectable contraceptives, and the current and future anticipated position of Depo-Provera®, generic DMPA, and depo-Uniject™ in that market. The information was used by USAID to inform initial product procurement and price negotiations with Pfizer.
- The depo-Uniject™ team completed research and analysis to document the product's value proposition and identified the highest-value service delivery and country settings for introduction and scale-up. The presentation includes supporting evidence documenting where and how depo-Uniject™ can increase access to injectable contraceptives, optimize use of donor resources, and lead to increased contraceptive prevalence and continuation. An analysis of market and service delivery opportunities in 21 countries with a framework for evaluating the current status of non-clinic or community-based access to injectable contraceptives was also completed.
- The SILCS Diaphragm team evaluated three colorant formulations and selected the Gayson colorant as the most acceptable for color match, cost, and likelihood for being biocompatible. Discoloration and chemical resistance testing was then conducted with the Gayson colorant. The team developed a biocompatibility verification plan that provides rationale for the testing needed to validate the safety of the new colorant formulation.
- The microbicides delivery systems team and CONRAD conducted a site initiation visit at Profamilia in the Dominican Republic, and subsequently the comparative applicator study was initiated. The enrollment goal of 25 women was reached by the end of March.
- Shanghai Dahua Medical Apparatus Co. (Dahua) received European regulatory approval for the CE marking of the Woman's Condom in December 2010. Dahua created a brand name and associated packaging and design elements for selling the product in the private sector in China.
- Interest is high regarding the Woman's Condom; more than 20 commercial inquiries for the product have been received from various countries. These inquiries are an indication of demand that could be addressed once regulatory approvals and in-country registrations are achieved, production capacity is increased, and distribution and marketing channels are identified.
- The chlorhexidine (CHX) for umbilical cord care team worked with collaborating partners and the Bangladesh government to organize and convene a results dissemination meeting, followed by a series of meetings with representatives from key medical associations in Dhaka. The outcome identified several policy barriers. Subsequently, planning for the introduction of CHX in Bangladesh has been put on hold since national policymaker consensus has not yet been reached about the use of this product.
- Planning for a regional dissemination meeting on the final CHX main trial results is building momentum; a Bangladeshi team of policymakers will attend this meeting with the aim of reinvigorating the policy dialogue in Bangladesh and elsewhere in the region.
- Instituto Biológico Argentino's (BIOL's) World Health Organization (WHO) prequalification application for oxytocin in the Uniject™ prefilled injection system (oxytocin-Uniject™) and in ampoules was found to be complete and sufficient in terms of product safety and efficacy. The next milestone in this process will be a WHO on-site assessment at BIOL's facilities.
- HealthTech staff had very positive meetings with the United Nations Population Fund's (UNFPA) Latin American regional office in Panama. UNFPA subsequently asked the team to propose an initial phase of evaluation and introduction for community use of oxytocin-Uniject™ in three UNFPA priority countries: Bolivia, Guyana, and Haiti. HealthTech was invited to present oxytocin-Uniject™ at the UNFPA regional meeting of all Latin American countries scheduled for June 2011.

- WHO's Making Pregnancy Safer staff submitted a request for a change in specifications for oxytocin in the WHO Essential Medicines Model List that if approved by the Expert Committee will make it easier for countries to consider oxytocin-Uniject™. PATH, BIOL, and the Guatemalan Society of OB/GYNs all submitted letters of support for this proposed change.
- The HealthTech team working toward a systematic architected rational approach (SARA) to planning, managing, and acquiring software products in global health presented SARA outputs and accompanying methodology at an international collaboration of global health informatics experts in Seattle, called the Collaborative Health Platform Meeting and hosted by the Bill & Melinda Gates Foundation.
- Testing of version 2 (Beta) of Cold Chain Equipment Manager (CCEM) was completed with national data from Kenya, Nicaragua, and Uganda and the user documentation was completed. The team then assisted Kenya, Uganda, and Zimbabwe in completing national cold chain inventories and entering data into CCEM.
- HealthTech staff completed the field introduction of CCEM version 2 to the Department of Vaccines and Immunization (DVI) in Kenya. A country introduction workshop was subsequently held for DVI Kenya and teams from Ethiopia and Malawi in Nairobi, Kenya.
- HealthTech's anemia etiology tool team is working to provide proof of concept that reticulocyte hemoglobin could be measured with a bread-board device. The team selected the magnification, identified the transmission light source intensity at that magnification, established the calibration curve for the transmission light source, and then determined the magnification based on size-calibrated particles and the dimensions of field of view at the selected magnification. These activities were followed by preparation and validation of red blood cell (RBC) reagents comparing hemoglobin concentration determined from RBCs to hemoglobin in solution, and determination of time dependence of sedimentation, staining, and RBC viability.

Element: Family Planning and Reproductive Health

Exploring cost reduction of levonorgestrel-releasing IUD

Goal of project

This project explored opportunities for expanding access to a lower-cost levonorgestrel-releasing intrauterine device (LNG-IUD). This included exploring strategies for expanding access to the existing product as well as development efforts underway to validate and bring to market a lower-cost version of a hormonal IUD. This project fits within the goal of expanding access to underused reproductive health technologies.

Status of project as of March 2011

The scope of this project is nearly complete. We are drafting a report to summarize the interviews and research conducted through this project; the report will include summary findings and recommendations. We expect the final report will be completed in June 2011.

We confirmed that several initiatives are underway, each of which aims for some version of an LNG-IUD. We identified hurdles that each of these initiatives must address, including clarifying the technology innovation, establishing production, navigating the patent protection landscape vis a vis the prior art, securing funding for clinical trials required for a full premarket application with the United States Food and Drug Administration and understanding the regulatory requirements. Medicines360, a nonprofit pharmaceutical company from the San Francisco area, has come farthest to overcome these hurdles. They navigated the regulatory strategy that allowed them to move very quickly to Phase II/III clinical trials, they are managing production, and they have secured funding. Their current funding is targeted to develop, test, and bring to market a lower cost LNG-IUD that will improve access for public-sector family planning programs in the United States. However, they may be well positioned to improve access to this technology in low- and middle-income countries in the future.

A key obstacle that does not seem to have been addressed is establishing a stronger sense of the value proposition for this technology, especially for women in low-resource settings. Even at reduced cost projections, the LNG-IUD will be more expensive and provide fewer years of protection than the Copper T IUD. The LNG-IUD clearly is an improved IUD technology that offers additional health benefits, such as reduced bleeding. Whether those additional health benefits make a compelling case, and whether women in developing countries who would benefit from reduced bleeding are the same women who would be likely IUD users, remains to be seen. We believe that before the public sector will invest in bringing even a lower-cost version of this technology to low-income countries, additional work is needed to quantify the health impact, identify in which markets and market segments the technology would be most impactful, and assess this potential impact relative to the health priorities of that country or region.

Achievements and progress in the past six months

- Met with staff from Medicines360 to learn more about the progress of their LNG-IUD product, which is currently being tested in a Phase II/III contraceptive effectiveness study in the United States. We learned about their strategy for developing and bringing this product to market in the United States and discussed potential developing-country markets.
- Began drafting a final report, which contains a summary of our findings and recommendations as informed by a literature search and several months of discussions with LNG-IUD developers, donors, and advocates.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Complete the final report.

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

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 system (hereafter called depo-Uniject) 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 2011

During the past six months, HealthTech has continued to play a key coordination role in the development and implementation of the USAID work plan for the rollout of the product. In addition, we have been able to significantly leverage funding provided by the Bill & Melinda Gates Foundation for the Planning for Introduction of depo-subQ provera 104 in the Uniject Injection System project to generate and share market information and analysis that is directly relevant to USAID procurement and planning decision-making.

HealthTech has remained in close communication with Pfizer to document and communicate up-to-date registration timelines. Pfizer expects to receive approval in the second quarter of 2011 for depo-Uniject from the Medicines and Health Care Products Regulatory Agency (MHRA) in the United Kingdom. Registration filings in USAID priority countries will follow MHRA during 2011, with the first in-country registrations expected in the first or second quarters of 2012.

In the area of research, final results from the ongoing pharmacokinetics (PK) study for subcutaneous administration in the upper arm are expected in July 2011 (implemented by Family Health International [FHI], funded by the Bill & Melinda Gates Foundation). The acceptability studies in Uganda and Senegal (implemented by FHI under PROGRESS) are expected to begin in August 2011 following results of the PK study, with a Kenya acceptability study beginning in the fourth quarter of 2011 (also implemented by FHI, funded by the Bill & Melinda Gates Foundation). HealthTech is developing the training materials for each of these studies. Materials for the Uganda study are in the final phases of testing, and lessons learned here will be used to inform final versions of the materials for Kenya and Senegal.

Achievements and progress in the past six months

Project Management and Coordination

- Maintained a comprehensive, multi-partner work plan and timeline for the USAID global pre-rollout activities for depo-Uniject; tracked and communicated critical path activities on a routine basis.
- Maintained 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.
- Prepared detailed, monthly project status updates and facilitated monthly discussions with USAID and the Bill & Melinda Gates Foundation regarding shared objectives and coordination of project activities. Consolidated project leadership of depo-Uniject projects at PATH (USAID and Bill & Melinda Gates Foundation funded) under a single project director to better leverage resources and increase effective information gathering, partner collaborations, and communications at both global

[1] depo-subQ provera 104 is a trademark of Pfizer.
[2] Uniject is a trademark of BD.

and country levels. Encouraged and expanded USAID and Bill & Melinda Gates Foundation planning interactions to effectively align program objectives and leverage funding toward completion of shared objectives.

- Met with FHI on a biweekly basis to review progress on acceptability study planning, align with training materials development, and contribute to study problem solving and study implementation planning. Communicated acceptability study status to USAID on a biweekly basis.
- Facilitated a monthly teleconference with Pfizer to maintain current status updates regarding product registration approvals and processes and reviewed information with USAID on a biweekly basis.
- On November 9 and 10, 2010, PATH and FHI met in Washington, DC, to coordinate the details of implementing acceptability studies, and in particular the Kenya study that is being supported by the Bill & Melinda Gates Foundation, along with parallel operational research/facility studies in all three countries. PATH also met with USAID on the same trip to coordinate project activities and to review and obtain input on the proposed PATH/FHI-coordinated acceptability study and operational assessment plans.
- In December 2010, facilitated initial discussions with FHI and Pfizer to establish requirements under Pfizer's Investigator Initiated Research process and to plan logistics for product delivery for the upcoming acceptability studies.
- Participated in the global Technical Advisory Group (TAG) meeting for introduction planning for depo-Uniject, held in Seattle on February 15 and 16, 2011. Presented information to the TAG on the critical path for pre-rollout introduction planning, including regulatory and research activities.
- Prepared targeted communications for the USAID Office of Population and Reproductive Health to disseminate to USAID missions. These materials included updated information regarding product details, research activities, regulatory status, and product availability.

Training Materials Development

- In close coordination with FHI, completed draft training materials for facility- and community-based health providers with prior experience delivering injections to be used for acceptability studies in Uganda and Kenya. Developed first draft Senegal training materials with finalization pending the confirmation of study details. Delivered materials to USAID for comment and facilitated feedback meetings in October 2010 and February 2011.
- Conducted clinical review of the Uganda training materials with clinical representatives from the Uganda Ministry of Health and FHI. Following clinical review, PATH completed formal pretesting of these materials and integrated the results into the final materials for Uganda and draft materials to be tested in Kenya.

Product and Market Analysis

- Prepared and delivered background information for USAID concerning the global market for injectable contraceptives, and the current and future anticipated position of Depo-Provera®, generic DMPA, and depo-Uniject in that market. The information was used by USAID to inform initial product procurement and price negotiations with Pfizer.
- Completed research, analysis, and presentation to document the depo-Uniject value proposition and identified the highest-value service delivery and country settings for introduction and scale up. Developed a comprehensive presentation with supporting evidence documenting where and how depo-Uniject can increase access to injectable contraceptives, optimize use of donor resources, and lead to increased contraceptive prevalence and continuation. Completed an analysis of market and service delivery opportunities in 21 countries with a framework for evaluating the current status of non-clinic or community-based access to injectable contraceptives, which serves as a pivotal strategic indicator of the potential impact of depo-Uniject on injectable access. Presented this information to key stakeholders, including the Bill & Melinda Gates Foundation, Pfizer, USAID, and other members of the global TAG.

- Selected Applied Strategies to conduct a detailed manufacturing cost analysis/cost of goods sold analysis (COGS) for DMPA injectable contraceptives (funded by the Bill & Melinda Gates Foundation). We expect this analysis to provide insights into the potential evolution of DMPA injectable contraceptive cost structure and pricing across a number of producer, product, and presentation scenarios, with particular emphasis on pricing for procurement by international donor agencies such as USAID and the United Nations Population Fund (UNFPA) as well as for national governments in developing countries.
- Interviews were conducted with key stakeholders in several countries to contribute to the development of recommendations for secondary packaging, marking, and labeling for depo-Uniject. Contributing stakeholders included Crown Agents, John Snow Incorporated, ministry of health reproductive health program managers, and other community-based networks such as International Planned Parenthood Federation (IPPF) and Marie Stopes International (MSI), primarily in Malawi, Pakistan, and Tanzania.

Problems encountered and actions taken to resolve them

Initial plans to conduct limited testing of training materials in Uganda for both the Uganda and Kenya studies needed to be changed to accommodate additional stakeholder input in both countries. While creating unexpected work and adding to the expense of developing training materials, increased engagement should ultimately result in better support for the studies themselves. We expect that similar levels of effort will be required before the Senegal materials can be finalized.

Uncertainty around product price and procurement has limited meaningful engagement with stakeholders outside of USAID, particularly at the country level, until there is more clarity around these issues. HealthTech has leveraged meetings of the oxytocin-Uniject global TAG to share project status with representatives from IPPF, MSI, Population Services International, UNFPA, USAID, and the World Health Organization. We have also worked with USAID to update messages about the product status to USAID missions.

Next steps and milestones expected in the next six months

- Continue to act as the coordinating liaison among BD, Pfizer, USAID, and the planning and introduction partners to ensure effective communication, coordination, and timely availability of the product for acceptability studies and global rollout. Identify activities, responsibilities, and due dates for implementation and follow up with responsible parties to ensure implementation.
- Monitor and communicate critical path milestones to USAID and other select stakeholders.
- Monitor and document registration timelines and communicate across stakeholder groups for planning purposes; analyze risks and develop contingencies related to registration and product supply.
- Complete training materials for acceptability studies with depo-Uniject that FHI will conduct in Kenya, Senegal, and Uganda.
- Facilitate periodic phone conferences and meetings with BD and Pfizer for updates on regulatory status, manufacturing scale-up, and resolution of any product technical challenges.
- Convene and facilitate biweekly calls with USAID to coordinate work plan activities and monthly meeting with both USAID and the Bill & Melinda Gates Foundation.
- Complete the COGS analysis and present findings.
- Deliver initial recommendations to USAID for product configuration issues (secondary packaging, inserts, possible bundled disposal boxes, etc.), based on in-country interviews and analysis.
- Full European Medicines Agency regulatory approval and issuance of the certificate of a pharmaceutical product from the manufacturing country of Belgium is a key regulatory milestone expected in the next six months. We hope that registration filings in USAID priority countries will begin in the third quarter of 2011.

SILCS Diaphragm commercialization

The following six HealthTech reports describe projects under way that prepare for commercialization of the SILCS Diaphragm. These projects are:

1. SILCS Diaphragm health system assessment
2. SILCS Diaphragm label comprehension study
3. SILCS Diaphragm over-the-counter strategies
4. SILCS Diaphragm partnerships and market development
5. SILCS Diaphragm production scale-up assistance
6. SILCS Diaphragm regulatory submissions

SILCS Diaphragm health system assessment

Goal of project

The goal of this project was to characterize and assess policy, programmatic, regulatory and consumer issues that may impact the SILCS Diaphragm introduction in a low-resource setting. This project also helped identify the steps needed to raise awareness about this new product for key country-level decision-makers, such as reproductive health decision-makers, providers, and potential users.

Status of project as of March 2011

This project is complete. Results from the project were presented at a dissemination meeting in Kampala, Uganda, on November 24, 2010. Twenty participants from various fields, including the Ugandan Ministry of Health, local nongovernment organizations (NGOs), the University of Makerere, service providers, and advocacy representatives were present. The consultants' final report, which includes results from 31 focus group discussions and 53 stakeholder interviews across three sites as well as feedback from stakeholders who attended the dissemination meeting, has been received by HealthTech. Key findings from this assessment include the following:

- An alternative to nonoxynol-9 must be identified before a SILCS Diaphragm introduction in a developing-country setting is feasible.
- The capacity of existing family planning systems to consider introducing a new method is limited. Despite acknowledging that the single-size barrier addresses a gap in the method mix and would improve options for women who cannot or do not want to use hormonal methods or IUDs, family planning providers and government decision-makers suggest introducing the SILCS Diaphragm through the private sector or the nonprofit NGO sector. They want to see evidence that women can use this method and will want to use this before considering committing to introduction.
- The groups who are most interested in introduction have the least amount of power to influence this change. Decision-makers in Kampala discount rural women's ability to use the SILCS Diaphragm. Women and providers in rural settings, however, are more confident they could find strategies to use the SILCS Diaphragm, wash, and store it between uses.

Achievements and progress in the past six months

- Conducted a dissemination meeting in Kampala and presented results of the health system assessment to key stakeholders. Incorporated stakeholder feedback into the final report.
- Completed the final report which includes background on the status of family planning in Uganda, consumer attitudes about family planning, strategies for introduction, the policy and regulatory environment, a stakeholder analysis, and strategies for education and communication.
- Developed an abstract that is being submitted to the Best Practices in Family Planning conference to be held in Dakar, Senegal, in November 2011. (If the abstract is selected for presentation, HealthTech

will seek funding from other donors to support one of the Ugandan researchers to travel to Senegal to present.)
- Drafted a manuscript to share study findings. The manuscript will be submitted to the *African Journal of Reproductive Health*.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

None.

SILCS Diaphragm label comprehension study

Goal of project

The goal of this project is to implement a label comprehension study that will be submitted to the United States Food and Drug Administration (USFDA) as part of the 510(k) application for market clearance. Data from this study are required as part of the USFDA's review of the SILCS Diaphragm as a potential over-the-counter (OTC) consumer product in the United States.

Status of project as of March 2011

This project is delayed but is on target to be completed before the end of the HealthTech IV term, and data will be submitted to CONRAD for use in the 510(k) application.

During the past six months, HealthTech staff and California Family Health Council (CFHC) developed the study protocol, related study questionnaires, and the package labeling that will be evaluated in this study. These have been reviewed by CONRAD staff and finalized. HealthTech submitted the protocol to CONRAD who will submit it to the USFDA for their review and comment. HealthTech staff worked with CFHC, CONRAD, and the product commercialization partner to develop the label packaging that meets USFDA specifications that will be tested in this study.

The USFDA considers "labeling" as information available both inside and outside of the box and used by the provider and/or consumer to assess indications, contraindications, and warnings for product use. Printed instructions for use will be packaged inside the box. These already have been tested for comprehension in studies in the Dominican Republic, South Africa, Thailand, and the United States. Additionally, participants in the SILCS Diaphragm pivotal study implemented by CONRAD in the United States used these instructions to learn insertion and correct positioning without additional coaching, so we feel sufficient testing of the instructions for use has already occurred. Thus the label comprehension study will focus on the messages on the outside of the package box only. The study will specifically recruit low-literacy women to ensure the key messages are understood by this vulnerable population in the United States, which is a key concern for the USFDA based on the conversation we had with them in 2009 when we first engaged USFDA about requirements for an OTC application.

Achievements and progress in the past six months

- Developed SILCS Diaphragm outer package labeling that will be tested in the upcoming label comprehension study.
- Drafted study protocol and related study documents and submitted to CONRAD.
- Revised study protocol based on comments received from USFDA recommending the inclusion of face-to-face interviews.

Problems encountered and actions taken to resolve them

USFDA was slow in responding to the supplement to the SILCS Diaphragm investigational device exemption (IDE) that PATH and CONRAD submitted in July 2010. The supplement summarized data available to support the SILCS Diaphragm as an OTC device and outlined data expected from the Pivotal Study about fit and sizing. Since we were unable to get comments from USFDA about the sufficiency of the existing data, we drafted the label comprehension protocol without the benefit of USFDA feedback. We developed the protocol after consulting USFDA guidance documents about labeling OTC products, analysis of existing OTC labels, and guidance documents about label comprehension studies.

On the day CONRAD planned to submit the protocol to the USFDA, CONRAD received comments from the USFDA on the original submission. The USFDA raised concerns about the sufficiency of data already submitted and made recommendations about the label comprehension study. We already had incorporated almost all the recommended procedures in the study protocol. After consultation with our research partner, we revised the protocol to include additional interviews with a subset of participants to further test and confirm label comprehension as recommended by the USFDA.

Next steps and milestones expected in the next six months

- Implement the SILCS Diaphragm Label Comprehension Study.
- Analyze data from the label comprehension study. Recommend changes based on the study outcomes.
- Summarize data for submission as part of the 510(k) application to the USFDA.

SILCS Diaphragm over-the-counter strategies

Goal of project

The project goal was to develop a regulatory strategy for the SILCS Diaphragm as an OTC product and submit an application to the USFDA. The implications of an OTC product for introduction and marketing in various markets were also explored.

Status of project as of March 2011

This project is complete. CONRAD and HealthTech engaged in an informal consultation with the USFDA about data needed to prepare for an OTC submission at the time of the 510(k) application. We understood that USFDA would require a label comprehension study to test whether label messages are comprehensible to a range of audiences and provide sufficient instruction about intent and use of the device without a clinic visit. HealthTech developed a summary of currently available data and data expected when the SILCS Diaphragm Pivotal Study is completed. This summary was submitted to the USFDA in July 2010. CONRAD regularly checked with USFDA to see if comments were forthcoming. Due to the time constraints of needing to get the label comprehension study under way, we moved forward with protocol development.

Achievements and progress in the past six months

- We analyzed USFDA guidance regarding labeling for OTC products and label comprehension studies, and evaluated existing OTC contraceptive and reproductive health product labels in preparation for drafting the study protocol and developing the proposed label.

Problems encountered and actions taken to resolve them

The USFDA comments on the pre-IDE supplement in preparation for moving forward with the label comprehension study did not arrive in a timely manner. After consultation with CONRAD and the research partner, we moved forward developing the protocol based on the best guidance available.

Next steps and milestones expected in the next six months

None.

SILCS Diaphragm partnerships and market development

Goal of project

This project builds toward introduction and sustainability of the SILCS Diaphragm through the identification of qualified partners and through negotiated agreements that are required for commercialization of the SILCS device as a consumer product.

The product will be launched first in developed-country markets, which will enhance product sustainability and build experience among consumers and health care providers. This experience will facilitate SILCS Diaphragm introduction in low-resource countries in the future as they become ready to program this novel non-hormonal barrier device.

Status of project as of March 2011

This project is on target. The major milestone of identifying a commercialization partner and negotiating a commercialization agreement has been achieved, which paves the way for production scale-up and regulatory submissions scheduled before the end of HealthTech IV in 2011.

Previous HealthTech funding supported diaphragm market assessments and the implementation of commercialization strategic planning. Outputs of those activities suggested that initial launch of the SILCS device in developed countries would be useful to raise awareness and confidence in this device and to generate interest in introduction. In addition, our commercialization partner search identified more companies in Europe (rather than the United States) who expressed interest in distributing this product.

We evaluated potential commercialization partners and assessed alignment of their goals and capacity to implement the activities needed to move this technology from its current state to product launch. Through this process we narrowed our selection to one partner and signed a licensing agreement with them in December 2010. The commercialization partner has experience in the key areas we identified as necessary to launch this technology. They have a history of manufacturing and selling reproductive health products, expertise with regulatory applications, are committed to this product, and show understanding about the diaphragm market. The licensing agreement includes terms for a favorable pricing structure for public-sector distribution and a phased approach to introduction that will leverage assets established from early developed-country introduction to help facilitate future introduction in low-resource settings.

Achievements and progress in the past six months

- Conducted due diligence on the commercialization partner.
- Negotiated and signed a licensing agreement with this partner for commercialization of the SILCS Diaphragm.
- Worked with the commercialization partner to prepare for production scale-up, transfer of technical documents for the regulatory dossier submission to CE and USFDA, the label comprehension study, and developing additional educational tools to accompany the product launch.

Problems encountered and actions taken to resolve them

The caution HealthTech sees with this partner is that they are a small company, with distribution channels focused primarily in Europe and the Middle East. They do not have expertise or distribution channels that reach into developing countries. To mitigate this, the licensing agreement is limited in scope and focuses in a stepwise fashion on launching and establishing the product in a few key markets to raise awareness and experience with this product. During this time, HealthTech and other stakeholders need to work to identify and validate an alternative contraceptive gel that is appropriate for use in developing countries.

Once that is accomplished, the agreement has flexibility that allows HealthTech to collaborate with other distributors who reach into developing countries when markets and interest have been developed.

Next steps and milestones expected in the next six months

- Work with the commercialization partner to implement a work plan designed to bring the product to market in at least one country before the end of this project in 2011.
- Work with our commercialization partner on promotion materials, packaging, and training materials needed for product launch. Obtain feedback from early adopters of the technology in the launch country to modify materials if necessary. We will capture learnings that help support future use of the product in low-resource settings.
- Coordinate with the partner regarding the product label and packaging that will be used in the label comprehension study in the United States.

SILCS Diaphragm production scale-up assistance

Goal of project

This project provides technical and financial assistance to support SILCS Diaphragm manufacturing optimization and scale-up needed to prepare for product launch in 2011.

Funds from this project will be used in conjunction with financial investment from the commercialization partner and the contract manufacturer to transition the SILCS device production from a research and development effort to a validated production process. The goal of this project is to be ready for the regulatory audit by the European Community CE mark auditors and to be able to manufacture product to support the first phase of product introduction.

Status of project as of March 2011

The HealthTech technical team has worked diligently with Molded Rubber Products Corporation (MRPC), the contract manufacturer, and the commercialization partner to address steps toward production scale-up. MRPC in Butler, Wisconsin, has worked on a step-wise plan to optimize current tooling and manufacturing processes to prepare for efficient manufacturing and to meet cost targets. MRPC first focused on optimizing the spring mold and the spacer mold. Validation of the new molds is scheduled for April 2011 with a subsequent pilot production run scheduled for May 2011.

During this time, we continued work to validate a new colorant formulation for the SILCS Diaphragm and to validate this new colorant formulation—needed to address a discoloration issue identified in the inventory from the SILCS Diaphragm pivotal study. (It was confirmed that the discoloration was not a safety issue—discolored diaphragms are as strong on tensile testing as non-discolored diaphragms—but discoloration after use is a quality issue that will influence acceptability and therefore needed to be addressed.) The team evaluated three colorant suppliers to identify a formulation that matched the original SILCS Diaphragm color and we are presently conducting confirmatory validation testing including a review of the biocompatibility validation plan.

Achievements and progress in the past six months

- Completed an internal audit and update of critical files in the SILCS Diaphragm design history file in preparation for transfer to the commercialization partner.
- Fabricated two duplicate sets of the quality assurance/quality control jigs and dies. Transferred these to MRPC and to the commercialization partner along with all the test protocols. Facilitated review and training on testing procedures in preparation for production process validation and sign off.
- Evaluated three colorant formulations and selected the Gayson colorant as the most acceptable for color match, cost, and likelihood for being biocompatible.

- Conducted discoloration and chemical resistance testing of the SILCS Diaphragms with Gayson colorant.

Problems encountered and actions taken to resolve them

The discoloration issue was unanticipated and has caused delays in production process scale-up and unanticipated expense to the project. Tensile testing of SILCS Diaphragms at PATH uncovered inconsistencies in the test results compared to historical testing results on the same equipment. The technical team determined the tensile test machine software had been updated and this may account for the discrepancy in results. To address this, MRPC and PATH agreed to an extra round of tensile testing of samples to revalidate the PATH tensile test machine relative to the historical data.

Focusing on critical path activities has kept the technical activities moving forward. MRPC experienced another unexpected delay when the first set of optimized molds broke. Despite these challenges, the team anticipates a validation production run at MRPC in May 2011.

Next steps and milestones expected in the next six months

- Participate in production run validation at MRPC in May 2011.
- Participate in round robin quality assurance testing of samples from the May production run to validate test outcomes at MRPC and the commercialization partner.
- Coordinate with CONRAD, our commercialization partner, and MRPC regarding the ongoing plan for developing the 510(k) application.

SILCS Diaphragm regulatory submissions

Goal of project

This project supports the technical and regulatory assistance needed to develop and submit market registration dossiers for the SILCS Diaphragm that are needed for market approval by the USFDA and for the European Community (CE mark).

Our goal is to have both regulatory applications submitted and to have received at least one approval before the end of HealthTech IV. These approvals will allow the launch of this new product in developed-country markets, which is seen as a critical step for future introduction in developing countries.

Status of project as of March 2011

This project has made good progress. We successfully negotiated a commercialization agreement with the commercialization partner, which was a necessary step for moving forward with regulatory applications for marketing.

The commercialization partner is working to complete an application for CE mark approval first, since this does not require the results of the contraceptive effectiveness study as part of the dossier. The technical dossier compiled for the CE mark will give us a jumpstart on the files that need to be prepared for the USFDA 510(k) submission.

HealthTech staff updated and transferred the SILCS Diaphragm design history file to the commercialization partner and they compiled the SILCS Diaphragm technical dossier for review by the notified body in Europe for CE mark approval. A regulatory consultant reviewed the SILCS Diaphragm dossier and identified gaps where additional documentation is needed. We worked with the commercialization partner and MRPC to complete this documentation.

The commercialization partner arranged a CE audit at the MRPC facility so the MRPC ISO 13485 certification will be recognized by the CE Notified Body that will review the SILCS Diaphragm technical dossier. A CE audit of the commercialization partner's facility and the SILCS Diaphragm technical file is

scheduled for mid-April 2011. After that review, we will have an updated estimate of when the CE mark approval may occur.

After the CE review, we will turn attention to the 510(k) application. Our goal is to submit the USFDA application by June/July 2011. However, some of the biocompatibility test data will not be completed by that time. CONRAD shared preliminary safety and efficacy results from the SILCS Diaphragm pivotal study with the commercialization partner for purposes of the regulatory submissions.

Testing laboratories in both Europe and the United States have been contacted to assess the most efficient/cost-effective strategy for moving through this repeat biocompatibility testing. We will begin biocompatibility testing on the unambiguous tests while we await feedback from the USFDA on the more complex test protocols.

Achievements and progress in the past six months

- Updated the SILCS Diaphragm design history file and transferred it to the commercialization partner.
- The commercialization partner compiled the SILCS Diaphragm technical dossier. The file has been reviewed by a regulatory consultant and areas identified where additional documentation needed have been identified and addressed.
- The commercialization partner arranged for a CE audit of the MRPC facility. Their ISO certification now will be recognized by the European regulatory authority.
- HealthTech developed a biocompatibility verification plan providing rationale for the testing needed to validate the safety of the new colorant formulation. We are awaiting input from the USFDA on this plan.

Problems encountered and actions taken to resolve them

Changing the colorant formulation for the SILCS Diaphragm triggered the need to repeat biocompatibility testing. We developed a biocompatibility verification test plan that outlines the rationale and tests to validate the new Gayson colorant for the SILCS Diaphragm. We are asking for USFDA review of this test plan. Some of the tests are straightforward and commonly performed. Other tests are lengthy, expensive, and are not well characterized in the literature. We have asked the USFDA for input on those tests to confirm if they are necessary and for input on the protocols.

Biocompatibility of the colorant formulation, the production scale-up validation, and the label comprehension study results all are components of the 510(k) application. Those activities have been delayed. We propose to compile the 510(k) submission with the data that is available by June/July and submit to USFDA to get the review process initiated and then submit the validation study data as they become available.

Next steps and milestones expected in the next six months

- Initiate/continue biocompatibility testing and compile data for USFDA submission.
- Assist the commercialization partner with 510(k) regulatory application and draft substantial equivalence justification.
- With CONRAD, coordinate a pre-510(k) meeting with the USFDA to review our plan for the proposed regulatory submission.
- Compile data from the label comprehension study and submit to USFDA.
- Work with CONRAD, USFDA, and other stakeholders to validate an alternative contraceptive gel (such as Contragel) for use with the SILCS Diaphragm.
- Identify funding for the additional biocompatibility tests and for preliminary animal studies required to begin testing the safety of Contragel.

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 prevention technologies (MPTs) 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 2011

HealthTech is focusing on developing key messages that can be used by the Initiative for Multipurpose Prevention Technologies (IMPT) stakeholders to raise awareness and build support for MPTs. This is being done in conjunction with the Global Change Network (GCN) and in collaboration with the IMPT. HealthTech is also serving on the planning committee for the 2nd IMPT Symposium which will occur in November 2011. In this role, HealthTech is contributing significantly to the design, content, and format of this meeting.

Achievements and progress in the past six months

- Facilitated a message strategy discussion among the IMPT Advisory Committee on February 4, 2011, at an IMPT meeting convened in Washington, DC. The input from the Advisory Committee at this meeting formed the foundation for the draft messages developed by HealthTech.
- Developed draft messages and held a meeting among the Advisory Committee to share messages and gather feedback/input. HealthTech revised messages based on this input in preparation for field testing.
- Completed message testing interviews with 16 stakeholders representing key target audiences. To date these have included 5 funders, 6 researchers/product developers, 3 providers, and 2 advocates.
- HealthTech is serving as a member of the Symposium Planning Committee (IMPT meeting to be held in November 2011) and has contributed significantly to the development of the symposium.

Problems encountered and actions taken to resolve them

With our original budget, we had funding to conduct a limited number of interviews to test our draft messages. This was challenging, given the number of target audiences and the importance of getting these messages correct with the priority audiences. To address this challenge, HealthTech identified additional support for our message-testing activity, allowing us to conduct twice as many interviews as originally planned. This support was critical as it allowed us to gather input from many additional stakeholders that represent the key target audiences critical to the IMPT's success.

Next steps and milestones expected in the next six months

- Prepare a final report and presentation on key messages; both will be shared with the IMPT Advisory Committee.
- Make key messages available for use by IMPT partners in education and outreach.
- Continue to serve on the Symposium Planning Committee to shape content and format of the upcoming meeting.

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 2011

In January 2011, Profamilia in the Dominican Republic initiated the comparative safety study of a prefilled applicator and user-filled applicator delivering Tenofovir 1% gel. Profamilia has reached the target enrollment goal of 25 women, and all participants are expected to have completed study procedures by the end of May 2011.

HealthTech is continuing research and development of the SILCS Diaphragm as a controlled-release microbicide delivery device in conjunction with MIV-160. Drug release from polyoxymethylene spring core segments looks promising. The steps are underway to manufacture drug-loaded springs at Queens University Belfast (QUB) in the spring of 2011 in preparation for validating proof of concept of drug release from fully molded SILCS Diaphragms.

Achievements and progress in the past six months

- HealthTech and CONRAD conducted a site initiation visit at Profamilia in the Dominican Republic in November 2010.
- CONRAD submitted an amendment to their investigational new drug (IND) application with the US Food and Drug Administration for the use of Tenofovir 1% gel in the comparative applicator safety study.
- Initiated the comparative applicator study in January 2011; reached target enrollment goal of 25 women by the end of March.
- QUB, HealthTech, and MR Mold (based in California) designed and produced new custom molds for the SILCS Diaphragm controlled-release device to enable over-molding of microbicide-loaded spring cores; the molds were shipped to BOY, a company that is developing specialized injection molding equipment to overmold spring cores. The injection-molding equipment is due for installation at QUB in April 2011.
- Continued in vitro release testing with MIV-160; demonstrated good release from non-overmolded spring cores.
- In the process of negotiating a material transfer agreement (MTA) with the International Partnership for Microbicides (IPM) to gain access to dapivirine for use in the SILCS Diaphragm controlled-release feasibility studies.

Problems encountered and actions taken to resolve them

A number of technical issues relating to the design and development of molds and the overmolding process for the SILCS Diaphragm controlled-release product were encountered, leading to delays in the installation of injection-molding equipment at QUB. The largest technical delay was the design of the overmold—venting of the mold was particularly problematic. After numerous weeks of discussions and problem solving between QUB, HealthTech, and MR Mold, these key technical problems have been resolved. New overmolds are being delivered for installation on the BOY injection press for final testing. BOY will ship the tested equipment to QUB in Belfast (delivery expected in April 2011). QUB is also producing a new spring-core mold designed to better fit the equipment and allow for on-site production. These major technical obstacles have led to a delay in conducting the activities scheduled for fiscal year 2009. Given the limited timeframe remaining in HealthTech IV, and assuming delivery and installation of the Boy injection press in April 2011, we will focus activities on the key experiments and related

activities need to demonstrate feasibility of controlled release from intact overmolded SILCS devices with MIV-160.

Next steps and milestones expected in the next six months

- Profamilia will complete all study procedures for the comparative applicator study.
- HealthTech and CONRAD will conduct a close-out site visit at Profamilia.
- HealthTech and Profamilia will conduct data analysis, complete the study report, and prepare a manuscript for publication.
- Provide study documentation to CONRAD for future regulatory use for including a paper applicator in the IND for approval with Tenofovir.
- Liquid injection-molding machinery will be installed at QUB.
- Finalize MTA with IPM for access to dapivirine for testing with the SILCS Diaphragm.
- QUB will evaluate intimacy of interfacial contact between the thermoplastic spring -core and the overmolded silicone elastomer sheath, including assessing the potential for pretreatment of spring cores and mold modifications.
- QUB will compound POM copolymer with 1%, 5%, and 10% with and without MIV-160 and determine the maximum MIV-160 loading that does not cause drug re-crystallization and/or phase separation.
- QUB will manufacture spring cores with MIV-160.
- QUB will evaluate in vitro release characteristics and mechanical performance of MIV-160-loaded SILCS Diaphragms.
- Prepare final reports and publications to share findings from QUB testing.

SILCS Diaphragm microbicide delivery system

The next two HealthTech reports describe completed SILCS Diaphragm microbicide delivery projects. These projects are:

1. SILCS Diaphragm microbicide delivery system: couples' acceptability of alternate gel scenarios.
2. SILCS Diaphragm microbicide delivery system assessed through magnetic resonance imaging.

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

Goal of project

The goal of this study was to assess the acceptability of the SILCS Diaphragm as a microbicide delivery system during couples' use. Couples evaluated two gel scenarios—SILCS Diaphragm with single-sided and SILCS Diaphragm with double-sided gel delivery—and compared these to gel delivery from a vaginal applicator.

The outcome of this project was two-fold: (1) it identified a preferred scenario for gel application and (2) it provided a preliminary assessment of the impact of gel volume and gel loading on acceptability for the woman and her partner across a range of measures.

Status of project as of March 2011

This project is complete. Data analysis and the final report were completed in 2010. An article depicting study results will be published in the December 2012 issue of *Contraception*. The study will be closed out with the PATH Research Ethics Committee at the time of its annual review in May 2011.

All three scenarios received favorable ratings for ease of application, acceptability, and perceived effectiveness. Both female and male participants tended to rate the gel applicator significantly more favorably than either SILCS Diaphragm gel delivery scenarios for all attributes except messiness/leakage and effectiveness. Additionally, about 60 percent of female participants and about half of male participants preferred the gel applicator to either of the gel delivery systems using the SILCS Diaphragm. The preference for the SILCS Diaphragm scenario for pregnancy protection was statistically significant for both genders. Male participants were also significantly more likely to prefer the SILCS Diaphragm with a single-sided delivery system to the gel applicator for sexually transmitted infection (STI) protection.

Achievements and progress in the past six months

- Submitted a manuscript to the journal *Contraception* for publication.

Problems encountered and actions taken to resolve them

The vaginal applicator—included in this study as a baseline—may have obscured women's ability to focus on the SILCS device as a gel delivery system. Women's lack of familiarity with diaphragms and greater familiarity with the applicator may have contributed to their reported preference for the vaginal applicator over the SILCS gel delivery systems.

Participants shared significant negative feedback about the gel characteristics. Poor acceptability of the gel per se may have interfered with women's ability to assess the SILCS Diaphragm for gel delivery.

Since this study was designed as minimal risk—participants were already using contraception and were in a monogamous relationship for at least three months prior to enrollment—couples did not perceive themselves at risk of pregnancy or STIs. Most women in this study used hormonal methods and were satisfied with their method. Results may differ for other populations depending on their motivation for

protection. Additional studies among populations that more closely mirror the potential users are warranted.

Next steps and milestones expected in the next six months

None.

SILCS Diaphragm microbicide delivery system assessed through magnetic resonance imaging

Goal of project

This proof-of-concept study assessed the feasibility and acceptability of the SILCS Diaphragm as a microbicide delivery system using magnetic resonance imaging (MRI) and qualitative assessments. MRI scans were used to assess microbicide gel coverage in the upper and lower vagina using three gel delivery scenarios: (1) SILCS Diaphragm with a single-sided gel delivery, (2) SILCS Diaphragm with a double-sided gel delivery, and (3) gel delivery from a vaginal applicator.

In this crossover study among six women, each woman underwent an MRI scan at three time points: (1) immediately after gel insertion, (2) after simulated intercourse, and (3) six hours after simulated intercourse. Women reported on their experience with the different gel delivery systems via Computer Assisted Self Interview (CASI) and completed in-depth interviews at study closure. The microbicide BufferGel®, manufactured by ReProtect, was used in this study.

Status of project as of March 2011

This project is complete. The clinical study report was completed in 2010. The study has been closed out with the University of Pennsylvania and PATH Institutional Review Boards. A manuscript has been drafted and is being reviewed by the research team before being submitted to a peer-reviewed journal.

This study confirmed that single-sided and double-sided delivery of microbicide gel on the SILCS Diaphragm is feasible. Data from the MRI scans show that good gel coverage can be achieved with all three methods. The gel coverage at the different time points varies across the different gel delivery scenarios at the three time points. It is not known if these differences would be significant in terms of clinical outcomes.

MRI scans from the main portion of this study were difficult to interpret since surprisingly little gel was found on the MRIs from the SILCS Diaphragm gel delivery scenarios. Reviewing the CASI questionnaires, researchers identified that women reported problems using the gel sachet and delivering the entire dose onto the SILCS Diaphragm. A study extension was approved that allowed three women to repeat single-sided delivery of gel with the SILCS Diaphragm and double-sided delivery of gel with the SILCS Diaphragm using different gel packaging to make gel dosing more consistent. MRI scans after use with the different gel packaging are more in line with the images seen with gel delivery from a vaginal applicator.

Results from this study indicate that the gel packaging and the physical characteristics of the gel are important considerations that influence acceptability. If used for future packaging, gel sachets need to be easier to open and use.

Achievements and progress in the past six months

- Completed the final study report.
- Drafted a manuscript. It is currently being reviewed and revised before being submitted to *Contraception* for possible publication.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

None.

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, 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 2011

Shanghai Dahua Medical Apparatus Co. (Dahua), the manufacturer of the Woman's Condom, received CE marking at the end of 2010. They submitted a product dossier for regulatory approval in China and a dossier for review by the World Health Organization/United Nations Population Fund (WHO/UNFPA) Technical Review Committee. Our current plan for approval by the Chinese State Food and Drug Administration (SFDA) remains unchanged, with market clearance expected in 2011, to be followed by a product launch in China. HealthTech funding for fiscal year 2011 focuses on technical support to Dahua for regulatory applications, production scale-up, and quality assurance testing. In late 2010, the Dutch Ministry of Foreign Affairs awarded a four-year grant to PATH to support additional manufacturing scale-up, technical assistance, and market development in China and in one country in sub-Saharan Africa.

Achievements and progress in the past six months

- Dahua received European regulatory approval for the CE marking of the Woman's Condom in December 2010.
- Dahua created a brand name and associated packaging and design elements for selling the product in the private sector in China.
- Dahua began design and development of a web page that will be used for consumer education and sales in China.
- Interest is high regarding the Woman's Condom; over 20 commercial inquiries for the Woman's Condom have been received from various countries. These inquiries are an indication of demand that could be addressed once regulatory approvals and in-country registrations are achieved, production capacity is increased, and distribution and marketing channels are identified.
- With separate funding, PATH engaged a market research firm to landscape the current market for sexual lubricants in China and explore consumer attitudes toward sexual lubricants. Lubricant is a critical component of Woman's Condom use and acceptability, and there seems to be little consumer awareness of lubricants in China.
- Drafted the final report and manuscripts for two Woman's Condom studies in China (1) the performance and failure mode study and (2) the acceptability data from the couples use (acute failure mode) study.
- Collaborated with CONRAD and the National Institutes of Health in responding to the United States Food and Drug Administration (USFDA) regarding technical data needed to supplement the investigational device exemption (IDE) for the Woman's Condom.
- Dahua produced a Woman's Condom inventory for the National Institute of Child Health and Human Development Contraceptive Clinical Trials Network (NICHD CCTN) contraceptive effectiveness study in the United States. A total of 25,000 Woman's Condoms and lubricant were ordered for the study and delivered in four shipments. Three shipments have been received to date. Final shipment is scheduled for April 2011. Dahua also delivered 2,500 condoms for the CONRAD-sponsored trial in California.

- Identified and conducted additional biocompatibility and/or mechanical testing of the Woman's Condom per guidance from the USFDA in response to our IDE application for the NICHD CTTN contraceptive effectiveness study.
- HealthTech and Dahua staff attended the WHO/UNFPA Female Condom Workshop in Bangkok, December 7 through 10, 2010, to discuss issues associated with the effective design, production, quality assurance, clinical evaluation, prequalification, and procurement of female condoms. HealthTech staff also attended a special session on day four to discuss donor collaboration.
- Assisted Dahua to create and submit necessary documentation for regulatory approval by WHO/UNFPA for a technical review recommendation; all materials were submitted at the end of March 2011.

Problems encountered and actions taken to resolve them

Production scale-up and increased efficiency is critical to lowering the cost of the Woman's Condom. 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: in-house film production equipment for approximately US$500,000, ring/dot welder at US$750,000, automated mandrel handling and leak testing at US$500,000, and a high-volume cap stuffing machine, ranging from US$250,000 to US$500,000. We are assisting Dahua to identify and secure co-funding for this equipment. HealthTech is closely monitoring any potential changes in product specifications resulting from the manufacturing scale-up processes. Ideally, any product that is manufactured using scaled-up processes will remain within current product specifications.

As Dahua produces Woman's Condoms for clinical trials and begins to scale up the production, we are encountering and managing typical challenges associated with establishing commercial production of a product. As recommended by USFDA and WHO, we are working to characterize the final air burst properties based on lots produced for clinical trials, and we are continually monitoring product quality through systematic sampling as well as spot-checking and biocompatibility testing. Whenever technical problems are identified, we work to resolve them in collaboration with Dahua through investigations and corrections carried out by Dahua's quality management department and through expert consultation (William D. Potter is currently acting as manufacturing consultant to this project). Manufacturing processes and procedures are being improved accordingly.

Dahua has been recruiting for a marketing manager for nearly a year and to date has been unsuccessful in identifying an appropriate candidate. PATH and Dahua will continue to search for an appropriate candidate and will formulate additional creative approaches to establishing appropriate marketing expertise within Dahua.

Next steps and milestones expected in the next six months

- Approval by the SFDA for the Woman's Condom regulatory submission for market clearance in China, followed by Dahua's launch of the Woman's Condom.
- With separate funding, create global and country-based advocacy strategies to support Woman's Condom introduction.
- Submit manuscripts for performance and acceptability data from the couples use (acute failure mode) study in China to a peer-reviewed journal.
- Dahua will produce and deliver the final group of devices for the NICHD CCTN contraceptive effectiveness study in the United States (25,000 Woman's Condoms and lubricant).
- Dahua will move Woman's Condom production into their new factory in the summer of 2011.
- Identify and conduct any necessary additional biocompatibility and/or mechanical testing of the Woman's Condom per guidance from the USFDA in response to our IDE application for the NICHD CTTN contraceptive effectiveness study.

- Perform a pre-USFDA inspection audit of Dahua to verify factory quality systems and ensure they meet international quality production standards, if the USFDA deems it necessary for the NICHD CCTN study.

Element: Maternal and Child Health

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 2011

Planning for the introduction of a CHX product in Bangladesh has been put on hold since national policymaker consensus has not yet been reached about the use of this product. Planning for a regional dissemination meeting on the final CHX main trial results, tentatively scheduled for August/September 2011, is building momentum; a Bangladeshi team of policymakers will attend this meeting with the aim of reinvigorating the policy dialogue in that country and elsewhere in the region.

Achievements and progress in the past six months

- Worked with Saving Newborn Lives to develop a policy brief about CHX for global dissemination.
- Worked with collaborating partners and the Bangladesh government to organize and convene a results dissemination meeting, followed by a series of meetings with representatives from key medical associations in Dhaka in early December 2010. The outcome identified several policy barriers.
- Participated in a video conference to discuss presentation materials for the Nepal dissemination meeting.
- HealthTech took the lead in planning a regional dissemination meeting in Nepal which is now tentatively scheduled for August/September 2011.
- Created and submitted a letter to the World Health Organization (WHO) Department of Medicines Policy and Standards requesting changes to the CHX formulation (gel and liquid) listed in the WHO Essential Medicines List due to commercial availability of a CHX product. HealthTech will provide guidance to partners on letters of support for this effort.
- Submitted a form to include CHX in the WHO compendium of innovative technologies that address global health concerns.
- Continued to liaise with the potential CHX manufacturer (BIBCOL) in India regarding a possible collaboration.

Problems encountered and actions taken to resolve them

The Bangladesh dissemination meeting did not have the expected outcome of catalyzing product introduction and launch in that country. To address this, we revised our introduction strategy to focus more on policy dialog and advocacy. The current approach is to not move forward aggressively in Bangladesh now and wait for the Nepal dissemination meeting to invigorate the Bangladeshi delegation.

The Nepal dissemination meeting has been rescheduled at the request of the Nepal Ministry of Health, as they want to collect data on their pilot implementation project so they can present it at the meeting. The new tentative date in August or September 2011 will allow for the randomized control trial results to be published as well.

Next steps and milestones expected in the next six months

- Finalize the report from the demand assessment study in Bangladesh and report final results to our partners.
- Finalize the report describing the relative advantages of various regulatory pathways for global introduction of CHX product including US Food and Drug Administration, European Community, and individual country/regional approaches.

- Continue to liaise with the potential CHX manufacturer (BIBCOL) in India regarding a possible collaboration.
- Identify a firm or consultant and conduct search for potential manufacturers that can market a CHX product in India (as an alternative option to BIBCOL) and subsequently in other regions.

Gentamicin in the Uniject™ prefilled injection system

Goal of project

The goals of this project are to create a sustainable supply of gentamicin in the Uniject™[1] prefilled injection system (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 2011

The field evaluation of gentamicin-Uniject in Nepal is complete; results suggest that using gentamicin-Uniject as part of community-based management of neonatal sepsis is feasible and acceptable to health workers and the community. The Argentine pharmaceutical manufacturer, Instituto Biológico Argentino (BIOL) has an inventory of the appropriate empty Uniject product and gentamicin raw materials for production of additional supply if required.

Achievements and progress in the past six months

- Drafted two manuscripts of Nepal study results for submission to peer-reviewed journals; the first article focuses on feasibility and acceptability of using gentamicin-Uniject for community-based neonatal sepsis treatment, the second focuses on the training and supervision of female community health volunteers to conduct community-based neonatal sepsis treatment with gentamicin-Uniject.
- Finalized and disseminated the findings from the gentamicin-Uniject field evaluation in Nepal. Submitted the manuscript on feasibility and acceptability to the *Journal of Perinatology*; it is currently under review.
- Convened a follow-up meeting with USAID to discuss action items from the June 2010 consultative meeting.

Problems encountered and actions taken to resolve them

Identification of an appropriate location for a second field evaluation of gentamicin-Uniject to assess impact on coverage of treatment has been challenging. We will continue to work with our colleagues at USAID to identify an optimal site.

Next steps and milestones expected in the next six months

- Submit a manuscript, in collaboration with BIOL, on compatibility/stability test results of the gentamicin-Uniject product for publication in a peer-reviewed journal.
- Submit remaining manuscript (training and supervision of female community health volunteers to conduct community-based neonatal sepsis treatment with gentamicin-Uniject) for publication in a peer-reviewed journal.
- Conduct stakeholder and policymaker interviews in a variety of countries to determine the feasibility and level of interest in integrating the gentamicin-Uniject product into current neonatal health programs
- Based on the outcome of the stakeholder interviews, develop guidance for the most appropriate scenarios/settings for using the gentamicin-Uniject product.
- 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.

[1] Uniject is a trademark of BD.

- Commission BIOL to produce another batch of gentamicin-Uniject if the need for additional supply and appropriate funding are 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 Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, the Argentine drug regulatory agency, for registration of gentamicin-Uniject, a key step on the path to eventual commercial availability.

Intradermal vs. intramuscular delivery of influenza vaccine in immunocompetent elders

Goal of project

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

Prior studies of influenza vaccine delivered intradermally have not compared equivalent doses of vaccine administered by different routes. 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 response (CD4+ and CD8+ T cells) pre- and post-vaccination.

Status of project as of March 2011

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 older. Study results were provided in previous status updates.

Achievements and progress in the past six months

- Conducted data analysis of immune response against variant influenza strains after ID and IM administration of influenza vaccine. IM or ID route elicited similar antibody responses to variant influenza strains not included in the vaccine.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Preparation and submission of a manuscript reporting the findings related to cross-protection of ID influenza vaccine administration against variant strains, including the H1N1 pandemic influenza strain.

Neonatal resuscitation

Goal of project

The goals of this project are 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 2011

The focus of this project continues to be on meeting the objectives of the Global Development Alliance (GDA): Helping Babies Breathe (HBB). Specifically the aim is 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, and distribution/sale) in priority countries.

Achievements and progress in the past six months

- Participated in the semiannual meeting of HBB and the GDA Reduction of Newborn Mortality: Management of Newborn Resuscitation in March 2011.
- Published an article on the Indonesia neonatal resuscitation device evaluation that was conducted under other funding: Ariawan I, Agustini M, Seamans Y, Tsu V, Kosim MS. Choosing the appropriate neonatal resuscitation device for village midwives. *Journal of Perinatology.* 2011:1–7.

Problems encountered and actions taken to resolve them

None.

Next steps and milestones expected in the next six months

- Conduct an inquiry into the status of resuscitation equipment and HBB training curriculum procurement and distribution; draft report and submit final recommendation to USAID.
- Design and conduct field evaluation of up to five neonatal resuscitator designs in collaboration with Laerdal and the Ethiopia Ministry of Health.
- HealthTech may conduct the following activities under the GDA memorandum of understanding to strengthen logistics systems and to create/increase demand for newborn resuscitation:
  - In collaboration with host governments, develop guidelines on how countries can purchase and maintain quality resuscitation device kits.
  - In collaboration with host governments, develop a strategy for a sustainable distribution system for resuscitation kits.
  - Transfer knowledge and experience about potential market barriers to a fully functioning global distribution system.
  - Create a strategy for how information about resuscitation kits will be disseminated internationally.
  - Provide inputs to the American Academy of Pediatrics sustainability strategy for the HBB 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 upon by alliance members.
  - Participate in semiannual alliance review and planning meetings.
- Prepare and submit a manuscript to an appropriate journal on the essential newborn care study in India, if possible.

Oxytocin in the Uniject™ prefilled injection system

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 system (hereafter called oxytocin-Uniject).

Status of project as of March 2011

The capability of oxytocin-Uniject manufacturers to respond to potential market demand with a high-quality product has made steady improvement. 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 registrations in Latin America. During this period, BIOL obtained one additional product registration, in Bolivia. This brings the total number of countries in which the product is registered by BIOL for commercial sale to five: Argentina, Bolivia, Guatemala, Honduras, and Paraguay. Registrations are pending in several other Latin American countries, and with leveraged support from the Bill & Melinda Gates Foundation funded Oxytocin Initiative project, PATH is assisting BIOL to obtain product registration in Ghana. Modest commercial sales of the product are underway in Argentina. The company is in the process of obtaining and installing new equipment for printing, labeling, and trimming that will directly impact the cost of production and will lead to more favorable pricing.

A second pharmaceutical manufacturer, GlandPharma (Gland) in India, has registered the product in India and has now produced its first commercial batch of oxytocin-Uniject for use in a planned study by the Indian Council on Medical Research (ICMR). The demand for the product in India is still uncertain, but Gland is in position to build production capacity to support future studies and potential introduction.

Kalbe Farma of Indonesia remains committed to initiating stability studies of its oxytocin-Uniject. These studies are key first steps toward making oxytocin-Uniject available as a commercial product in Indonesia. The filling machine to be used for this initial production has been delivered to the factory in Indonesia and is presently being prepared for pilot-scale production of the stability study product.

Progress on supply-side activities described above is parallel to demand generation activities which HealthTech staff is supporting through technical assistance and logistics support for product supply to pilot projects and studies in Ghana, Honduras, and Nicaragua. These activities provide actual experience with the product and generate information that can be used to inform country-level procurement decision-making, both in the pilot country and in others.

We are taking the following steps to generate additional product and market information.In close collaboration with the Indonesian Ministry of Health (MOH); MCHIP; the US Pharmacopeia; the National Institute of Health, Research, and Development; and The National Agency of Drug and Food Control, PATH has begun work to assess the quality of existing oxytocin in Indonesia. Results from this study will serve as evidence to review current policies regarding storage practices and conditions for oxytocin injections and address some key challenges for storage and handling. We are also conducting a market research study in Indonesia to understand the willingness to pay of private midwives (bidans) for oxytocin-Uniject. The market assessment will involve one-on-one interviews with approximately 200 bidans to obtain structured feedback on the recognized benefits and challenges associated with oxytocin-Uniject.

[1] Uniject is a trademark of BD.

In January of 2011, HealthTech engaged an independent consultant to begin a broad opportunity assessment and landscape analysis of 30 USAID priority countries, seeking to assess and prioritize country settings that have the most optimal combination of public health need, market size, and other factors that may enable and support successful introduction of oxytocin-Uniject. Findings from this work will be available in the second quarter of 2011.

Achievements and progress in the past six months

Supply-Side Achievements

- BIOL registered oxytocin-Uniject for commercial sale in Bolivia, bringing the total number of registrations in Latin America to five countries: Argentina, Bolivia, Guatemala, Honduras, and Paraguay. Several other registrations are pending.BIOL's World Health Organization (WHO) prequalification application for oxytocin-Uniject and oxytocin in ampoules was found to be complete and sufficient in terms of product safety and efficacy. The next milestone in this process will be a WHO on-site assessment at BIOL facilities.
- With funding provided by PATH from non-HealthTech sources, BIOL purchased a label applicator and trimming equipment. Delivery and installation are expected during the second quarter of 2011.
- BIOL delivered oxytocin-Uniject for use in the Honduras study. Product supply is ready for delivery for a study in Nicaragua, pending in-country registration of the product.
- Gland successfully completed production of its first commercial batch of oxytocin-Uniject. These units are planned for use in a study by ICMR.
- HealthTech staff visited Indonesia to work with Kalbe Farma to develop a work plan for oxytocin-Uniject development.

Demand-Side Achievements

- Finalized Honduras study plans and approvals with in-country training scheduled to start the first week of April 2011 and first enrollment in the study shortly thereafter. HealthTech staff continue to play a key role in technical assistance, planning, and training for these activities.
- HealthTech continues to provide technical assistance to the Guatemalan MOH for potential adoption of oxytocin-Uniject within the country's PPH-prevention strategy. At a meeting with HealthTech staff in December 2010, the Guatemalan MOH stated it is planning to introduce oxytocin-Uniject in a select number of provinces and has formed a task force to move this forward.
- HealthTech staff had very positive meetings in December 2010 with the United Nations Population Fund's (UNFPA) Latin American regional office in Panama. UNFPA's Latin American regional office has subsequently asked PATH to propose an initial phase of evaluation and introduction for community use of oxytocin-Uniject in three UNFPA priority countries: Bolivia, Guyana, and Haiti. UNFPA invited PATH to present oxytocin-Uniject at the UNFPA regional meeting of all Latin American countries scheduled for June 2011.
- Finalized the protocol for quality assessment in Indonesia of oxytocin as stored in various warehouse and clinic sites with our collaborators—the National Institutes of Health, Research, and Development (NIHRD); the Indonesian Food and Drug Monitoring Agency (BPOM); and United States Pharmacopeia (USP).
- Completed initial USP training in oxytocin analytical testing methods for NIHRD and BPOM staff in March 2011.
- Finalized a work plan for the market research study in Indonesia to understand the willingness to pay of private midwives (bidans) for oxytocin-Uniject. Data collection is scheduled for April 2011.
- HealthTech engaged an independent consultant in January 2011 to begin a broad opportunity assessment and landscape analysis for up to 30 USAID priority countries.
- WHO's Making Pregnancy Safer staff submitted a request for a change in specifications for oxytocin in the WHO Essential Medicines Model List that if approved by the Expert Committee that met in

March will make it easier for countries to consider oxytocin-Uniject. PATH, BIOL, and the Guatemalan Society of OB/GYNs all submitted letters of support for this proposed change.

Problems encountered and actions taken to resolve them

As of March 2011, Kalbe Farma had not yet started stability studies of oxytocin-Uniject due to unavailability of the table-top Uniject filling machine. HeathTech staff discussed this situation with BD Indonesia and with BD headquarters staff and were assured that they would deliver the needed equipment to Kalbe Farma by end of March 2011.

The large-scale community use study of oxytocin-Uniject planned for India under the Oxytocin Initiative project was not approved by the PATH Research Ethics Committee, and the project team decided not to pursue the trial further. This will result in a fairly large quantity (around 10,000 doses) of unallocated oxytocin-Uniject in inventory at Gland. HealthTech staff have initiated discussions between PATH India, BD India, and others to search for one or more suitable maternal health projects or programs in India that could make use of the Gland product.

Progress toward registration of BIOL's oxytocin-Uniject in Ghana and Mali has not progressed as expected. In Ghana, HealthTech staff have helped reestablish the commercial dialogue between BIOL and the Ghanaian distributor—Vicdoris. In Mali, HealthTech staff have provided technical support and product samples to MCHIP Mali, as they are leading the in-country efforts.

BIOL informed PATH that it does not expect to complete its production area renovations in preparation for the on-site WHO prequalification assessment until sometime during the first half of 2012. A HealthTech business and technical team will visit BIOL during the first week of April 2011 to better assess the situation.

Next steps and milestones expected in the next six months

Supply-Side Activities and Milestones

- Provide ongoing technical assistance to BIOL to prepare for WHO prequalification of oxytocin in ampoules and oxytocin-Uniject.
- Using independent pharmaceutical consultants, conduct a mock audit of BIOL facilities to prepare for a potential prequalification visit by WHO and document results.
- Assist BIOL, as needed, in the installation and testing of new semi-automated trimming, printing, and labeling equipment (purchased by PATH and BIOL using non-HealthTech funding). Complete the installation and validation processes.
- Supply product for the potential introduction in Mali and pilot studies in India (by ICMR) and Nicaragua (pending registration).
  Obtain new product registrations from the following Latin American countries: Costa Rica, the Dominican Republic, Ecuador, El Salvador, Nicaragua, Panama, Peru, and Uruguay. Initiate the registration processes in Ghana and Mali.
- Document three-year stability data from BIOL.

Demand-Side Activities and Milestones

- Complete the facility- and community-level studies in Honduras and disseminate the results.
- Assist BIOL in finalizing their public- and private-sector pricing strategies based on refined cost models and improved production processes.
- Complete the Indonesia oxytocin quality assessment and disseminate the results.
- Complete and document a market research study in Indonesia to understand the willingness to pay of private midwives (bidans) for oxytocin-Uniject.
- Initiate the pilot study in Nicaragua (pending product registration).
- Prepare and submit for publication the results of the Guatemala pilot introduction conducted in 2009.

- Finalize plans for product introduction in Guatemala.
- Deliver the results of the oxytocin-Uniject opportunity assessment and landscape analysis to USAID.
- The WHO Essential Medicines list will be revised for oxytocin from the currently restrictive "10IU in 1ml ampoule" to wording that will allow for consideration of prefilled syringe presentations such as Uniject (decision currently pending).
- Prepare a final report of products and findings from the oxytocin-Uniject project.

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 2011

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 secured two independent lots of these key reagents from commercial partners for research and development purposes. Research and development of the test continues.

Achievements and progress in the past six months

- Results with commercial-grade reagents correlate well to results with prototypical reagents.
- Assessment of commercial-grade reagents with human samples has begun.

Problems encountered and actions taken to resolve them

Research and development with well-characterized human samples has shown that the most recent prototype does not yield reproducible results and that extraneous protein may induce false-positive results. Research and development activities are continuing to determine the root cause as well as how to prevent false-positive results. Work is focusing on the optimal assay reagents and conditions as well as exploring sample preparation methods.

Next steps and milestones expected in the next six months

- Continue research and development using the commercially available reagents to develop iterative prototype tests.
- Evaluate the prototype tests with simulated (spiked) serum samples and clinically relevant samples then identify any areas that need additional research and development.
- As a final deliverable, complete a prototype rapid test that is capable of detecting antibodies to HPV type 16 or 18 as evaluated by testing simulated (spiked) serum samples and a limited set of clinically relevant samples.

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 2011

This effort has advanced to the documentation and validation stage in three discrete areas, each exploring some common and unique aspects of SARA. First, HealthTech has completed software development of the Cold Chain Equipment Manager (CCEM) software product based on applying industry practices and open source tools for the management of source code and the development process. CCEM version 2 (CCEM 2) has been field tested in Kenya with training completed with teams from Ethiopia and Malawi, and the quality and integrity of the data model and analytic components of CCEM have passed the beta testing phase. CCEM 2 is now available for downloading publically at no cost. Second, we applied SARA as a process to determine and document new and refined requirements for the SmartConnect project based on the version 1 prototype and produced a version 2 prototype of this solution. Finally, we expanded the application of SARA to determine and document system requirements in Tanzania to test their applicability for multiple health service program areas and to evaluate their usefulness beyond the tuberculosis (TB) program area.

Achievements and progress in the past six months

- Achieved beta 2 and final release candidate versions of CCEM 2.
- Completed a follow-up review of the use of the beta version of the CommCare mobile application including the use of data for decision-making.
- Expanded the scope of the requirements for scaling CommCare as a generalized mobile application and determining relevance of these requirements for maternal health program-specific health services.
- Presented the SARA outputs and accompanying methodology at an international collaboration of global health informatics experts in Seattle, called The Collaborative Health Platform Meeting and hosted by the Bill & Melinda Gates Foundation, March 23 and 24, 2011.

Problems encountered and actions taken to resolve them

As reported in the last semiannual report, the challenges faced in Tanzania include the need to raise additional funds to support a scalable deployment of a community health worker (CHW) solution for TB. While SARA was effective at determining user requirements, the system requirements became challenging due to larger system questions being presented. For example, is there funding and political support to deploy a CHW tool for TB case detection nationally? If so, how many CHWs might this involve? Over what time frame might additional workers be trained and equipped to use the CommCare solution? These questions pointed to the larger strategic planning context in Tanzania and go far beyond the success of the SARA process and the success of the technical pilot. These questions point toward stakeholder buy in, policy development, and securing adequate resources to support scaled deployment.

Next steps and milestones expected in the next six months

Complete SARA documentation:

- Draft a high-level development plan for the next version of CCEM.
- Complete the validation and refinement of the TB program user and system requirements produced in Tanzania in the maternal, child health, and nutrition program area.
- Complete field testing of the version 2 prototype of the SmartConnect solution.

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.
- 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, 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 2011

Cold Chain Inventory

The management information system (MIS) aspect of this program area has evolved significantly in this reporting period with the completion of the field introduction of the Cold Chain Equipment Manager version 2 (CCEM 2) software program, while continuing to inform and contribute to the project Optimize body of knowledge and strategy, and participating in Safe Injection Global Network and TechNet global meetings.

Cold Chain Technologies

We are undertaking the following projects with non-HealthTech sources of funding:
Freeze protection for passive carriers: The aim of this project is to demonstrate significantly improved freeze protection for vaccine carriers (cooled with non-conditioned ice packs) by retrofitting with a low-cost phase change material liner. The outcomes of this project will be data and technology sharing with the original manufacturers and policymakers as well as advocacy toward a World Health Organization performance, quality, and safety specification that includes specific, achievable freeze protection criteria. This project leverages emerging technologies and ultimately could result in a new class of ice-cooled carriers that allow for freeze protection and (as an unintended consequence) improved holdover. The early data is very encouraging.

Safe-Ice: This upstream research and development (R&D) project examines a novel freeze protection strategy and increased holdover without use of phase change materials (PCMs). The initial project activities underway focus on high-level simulation modeling that will inform downstream design work.

Free Piston Stirling Cooler (FPSC) Solarchill: As an alternative to traditional AC and DC compressors, FPSC offers some distinct advantages including temperature moderation and increased solar-day use. We continue to explore the comparative advantages of FPSC and have co-developed several functional prototypes undergoing evaluation.

Domestic fridge retrofit: We are currently looking for on-the ground partners to help demonstrate the improved freeze protection afforded by the addition of strategically placed PCM panels in domestic refrigerators. This project is in the concept stage, and we are anticipating low-level funding soon through the Health Innovation Portfolio to enable additional scope.

Outreach reconstituted vaccine cooler: This upstream R&D project is aimed at providing a simple tool that ensures adequate reconstituted vaccine cooling during vaccination sessions. We have developed

several prototypes and have data to support the concept. Further progress is contingent upon development of a consensus-driven product profile and engineering specification.

Achievements and progress in the past six months

Cold Chain Inventory

- Completed the field introduction of CCEM 2 to the Department of Vaccines and Immunization (DVI) in Kenya.
- Completed beta 2 version testing with national data from Kenya, Nicaragua, and Uganda.
- Assisted Kenya, Uganda, and Zimbabwe in completing national cold chain inventories and entering data into the CCEM.
- Held a country introduction workshop for DVI Kenya and teams from Ethiopia and Malawi in Nairobi in March 2011.
- Completed user documentation.
- Engaged in internal and external stakeholder discussions to solicit support for a long-term product management plan for CCEM, including a strategy to move to a web-based platform for version 3.
- Continue to collaborate with Hewlett Packard and the Clinton Health Access Initiative around design and development opportunities for future versions of CCEM.
- Completed an initial architecture assessment of the District Health Information System version 2 as a feasible option for routinely updating, transmitting, and storing facility-level data on vaccine refrigerator equipment.

Cold Chain Technologies

- Completed the solar autonomy tool manuscript and submitted it for publication. Successful publication will enable increased awareness of this important tool that was originally supported through HealthTech.
- Collected initial data on the vaccine carrier retrofit strategy which is very encouraging. We have shown substantial increase in freeze protection and holdover time by the addition of a low-cost PCM liner to off-the-shelf vaccine carriers.

Problems encountered and actions taken to resolve them

Cold Chain Inventory

Discussions with stakeholders have revealed that there is a perception that the cost of the national inventory of all cold chain equipment costs too much for the benefit to be realized in cold chain equipment planning. The approach to addressing this challenge has taken two parallel paths. First, resources have been identified to research the feasibility of reducing the size of the inventory from 100 percent to a smaller sample size—resulting in lower costs, and also to investigate alternative models and forecasts to understand the capacity and strength of the cold chain. The second approach is to assess the viability of building a web-based inventory system that will allow incremental updates from peripheral levels to ensure that the inventory remain valid and amortizes initial costs of collection.

With the achievement of milestones for CCEM 2 development, the emphasis shifts to the challenge of stakeholder support and adoption of sustainable support for deploying CCEM 2 to each country planning to introduce new vaccines where inadequate cold chain capacity presents a significant risk of vaccine introduction failure.

Cold Chain Technologies

The outreach reconstituted vaccine cooler project is on temporary hold as we were unable to derive a clear definition of a product profile and technical specification. We will continue to have key-stakeholder conversations as we try to gain clear objectives for this technology. Once these are achieved, design work can resume.

Next steps and milestones expected in the next six months

Cold Chain Inventory

- Cold chain inventories have been completed for Uganda and Zimbabwe, and we will conduct an initial introduction of CCEM and training to those countries.

Cold Chain Technologies

- Completion of bench testing for the passive carrier freeze protection strategy.
- Completion of Safe-Ice computational fluid dynamics simulations.
- Initiation of domestic refrigerator retrofit project.

Element: Nutrition

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. We have determined these requirements from informational interviews with stakeholders within each of the potential markets. More importantly, we have determined 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 now are working to determine the technological feasibility of developing the proposed tool.

Status of project as of March 2011

Claro Scientific LLC

Our main objectives for the Claro Scientific LLC (Claro) platform are to advocate for the development of field-worthy prototypes for assessment of performance for malaria and anemia detection, to inform Claro engineers on the desired characteristics of their prototypes through a form-factor study in a malaria-endemic country, to perform a market study to determine if the Claro platform can be a sustainable diagnostic platform in malaria-endemic countries, and to determine where the product will be placed within the health system to achieve the greatest public health impact.

To date we have engaged key stakeholders within diagnostic development at the Bill & Melinda Gates Foundation and at the Foundation for Innovative New Diagnostics regarding the promise of the Claro platform. We identified numerous funding opportunities and are aggressively pursuing each avenue in order to further product development. The Claro platform will be presented by Claro's founder at the Oak Ridge Conference for Diagnostics, and the HealthTech bio-engineer will present at an optics conference on the power of the Claro platform.

The form-factor study planning is in process, prototype components and data collection tools are currently being developed, and the PATH team should be in the field by June 2011. HealthTech and the CEO of Claro are collaborating on the market study and are currently refining the study objectives. The implementation of the market study is on track with project timelines.

Turner Applications

The objective for the Turner Application system was to provide proof of concept that reticulocyte hemoglobin could be measured with the breadboard version. The activities are divided into two phases (1) an in-house feasibility assessment in which the device would be built and preliminary experiments conducted to demonstrate the concept and (2) a clinical assessment to determine the accuracy of the breadboard system. The in-house feasibility assessment of the Turner Application breadboard system is near completion. By June 2011, we will challenge the system with clinical samples from anemic and normal whole blood samples that have had their reticulocyte hemoglobin characterized by an automated analyzer from an external quality assessment at a clinical laboratory at the University of Washington. If the precision, linearity, and correlation are acceptable, when future funding becomes available we will take the breadboard system to the field where more iron deficient samples can be acquired.

Achievements and progress in the past six months

Claro Scientific LLC

- Identified possible funding opportunities for product development and evaluation: the Biomeriuox Foundation, the National Institute of Allergy and Infectious Diseases, USAID, and the National Institute of Biomedical Imaging and Bioengineering.

- Submitted a successful application to present an oral presentation of the Claro platform at an optics Conference.
- Drafted the form-factor study protocol; finalized the research study questions, the data collection tools, the timeline, and budget. We also identified the form prototypes and study site.
- Drafted the market study and initiated the research objectives formulation. Acquired existing Intercontinental Marketing Services data for relevant market segments and drafted a survey to send to all PATH country offices that will identify procurement schemes and key decision-makers.

Turner Applications

- Ordered, received, and assembled all supplies for the breadboard system. Developed, procured, and evaluated the Image J software required for the breadboard system.
- Selected the magnification and identified the transmission light source intensity at that magnification. Established the calibration curve for the transmission light source. Determined the magnification based on size-calibrated particles and the dimensions of field of view at the selected magnification.
- Prepared and validated red blood cell (RBC) reagents. Compared hemoglobin concentration determined from RBCs to hemoglobin in solution. Determined time dependence of sedimentation, staining, and RBC viability.
- Decided on final whole blood dilution.
- Characterized flow cell carryover.
- Installed fluorescent light source and calibrated intensity.
- Characterized Advia Control on the breadboard system.
- Finalized the logistics for whole blood sample acquisition.
- Finalized the logistics for reference testing of clinical samples at the University of Washington.

Problems encountered and actions taken to resolve them

Claro Scientific LLC

The form-factor study was originally planned to occur in two sub-Saharan African countries. However, the scope of the activities that need to occur in each country were beyond what we had earmarked for this activity in the budget. Therefore, we decided to do a more in-depth analysis in one country that tapped into a broad range of end-users from various levels within the health system.

Furthermore, Claro had a technological breakthrough that allowed them to reach a much lower limit of detection for malaria diagnosis that pushed the boundaries of what is currently possible. This breakthrough enables the platform to theoretically be used for additional diagnostic applications such as bacterial and viral identification in various sample types. Although this is promising news, the superior lower limit of detection now requires a larger sample volume than was originally planned. This means that the product placement may now be limited to areas in which venipuncture is available. Claro is unsure if a platform that has an inferior lower limit of detection but is able to use a smaller sample volume from a finger stick is more beneficial than a platform that has a superior lower limit of detection for malaria and could be used for other diagnostic purposes but uses a larger sample volume that requires venipuncture. This has complicated the identification of end-users to interview and broadened the scope of research questions for the form-factor study. The decision to choose one platform over the other would require a stakeholder assessment prior to a form-factor study, which is not possible within our timeline, so we have decided to interview end-users that would use both platforms.

Turner Applications

The development of the Turner breadboard system has met with no problems in the feasibility phase. However, we have met with considerable obstacles for challenging the system in a field setting where iron deficiency prevalence is high. We had originally identified a field site in Kenya that was specifically looking at iron deficiency biomarkers but did not have the ability to measure reticulocyte hemoglobin, although they were attempting to get ethical approval to do so. This site selection had two major

obstacles. Foremost, was the acquisition of an automated analyzer to serve as the reference machine. The Kenya field site agreed to let us conduct the study if we procured the reference assay platform. Secondly, the Kenya site had not yet received ethical approval for the study and the enrollment of iron deficient children was spread over a lengthy period of time that did not fit within our project timeline. Because of these obstacles, we decided to look for other sites. To date, we have not located a suitable site that could achieve our goals within the HealthTech IV term, so we have decided to put this activity on hold for the present.

This left us with the problem of testing the system with samples with reticulocyte hemoglobin levels that spanned the entire range of physiological levels because the prevalence of iron deficiency anemia in Seattle is relatively low. To overcome this hurdle we contacted a blood collection service that is capable of providing us with samples from anemic donors as well as normal donors. Although this sampling is limited, it will provide us with the preliminary data needed for justification of taking the system to an endemic country for testing on human subjects with iron deficiency.

Next steps and milestones expected in the next six months

Claro Scientific LLC

- Implement the form-factor study, analyze the study results, and finalize the study report by September 2011.
- Finalize the market study research questions with Claro, send the survey to PATH country offices, and select sites for in-country research based on responses to the survey.
- Implement the market research study in at least two sub-Saharan African countries, analyze the results, and finalize the market study report by September 2011.

Turner Applications

- Perform in-house feasibility to determine if a light-scattering method is more appropriate than transmission by June 1, 2011.
- Conduct clinical sample evaluation including precision analysis, linearity assessment, and correlation with a reference assay by July 1, 2011.
- Plan a field evaluation of the breadboard system; identify an appropriate site, outline a shell protocol for field-site collaborators, and identify budgetary and contractual requirements by September 2011.

Skunkworks

Diagnostics

The African Network for Drugs and Diagnostic Innovation—diagnostic device technology transfer and capacity-building initiative

The objective of this initiative is to undertake diagnostic development, technology transfer, and related capacity-building initiatives to support the development of certifiable, commercially successful, and sustainable diagnostic device local manufacturing and distribution operations throughout Africa. Launched in Abuja in October 2008, the African Network for Drugs and Diagnostic Innovation (ANDI) is an African-led initiative under the legal umbrella of the United Nations Economic Commission for Africa. ANDI is a response to several global calls and declarations to support health and health research capacity in Africa. These calls highlight the relevance of health research and development to economic development.

The PATH Diagnostics Development Group was invited to attend and present at the 3rd ANDI Stakeholder Meeting in Nairobi, Kenya, after which PATH was invited to engage with ANDI. ANDI's director visited PATH's Seattle office as part of this initiative, and PATH, as the next step, will attend the upcoming ANDI Board of Directors Meeting in May 2011, wherein ANDI's first diagnostic companies identified for ANDI development support will be introduced to PATH.

ANDI and PATH are in the process of formalizing a collaboration through a memorandum of understanding. This development is timely as it has the potential to enhance and accelerate opportunities for capacity-building of African locally owned/locally operated diagnostic device manufacturing and marketing/distribution operations.

Capacity-building initiative at the Kenya Medical Research Institute manufacturing and production facility

The objective of this capacity-building initiative is to undertake commercialization activities for the creation of a certifiable and sustainable diagnostic device manufacturing and distribution facility at the Kenya Medical Research Institute (KEMRI). The KEMRI production facility is owned and lead by the Government of Kenya.

The PATH Diagnostics Development Group has been engaged with KEMRI since 2007 under the auspices of the Center for Point-of-Care Diagnostics for Global Health (GHDx) sponsored by the National Institutes for Health. Collaborative activities have included laboratory evaluations of KEMRI's HIV and hepatitis C diagnostic tests; due diligence visits by PATH personnel to the KEMRI facility in Nairobi, and participation by Dr. James Kimotho, General Manager of the KEMRI production facility unit, in a GHDx-sponsored training and fellowship program.

In October 2010, PATH attended a meeting for the release of "KEMRI Manufacturing Options Report" commissioned by the President's Emergency Plan for AIDS Relief, and to explore a possible role for PATH in a future effort to build capacity for diagnostics manufacturing and production at KEMRI.

Development of a recombinase polymerase amplification assay for pulmonary tuberculosis

The goal of this project is 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. We are now proceeding to develop a RPA TB assay with TwistDx as well.

The initial stage in the assessment of the assay after establishing its sensitivity on highly pure TB DNA was to screen the DNA extracted from bacterial pathogens associated with respiratory diseases. The Washington State TB Reference Laboratory was a collaborator in this, and further work to assess the performance of the assays on clinical specimens derived from patients who were identified as being TB positive by a variety of methods. The species used covers a range of gram-positive and gram-negative pathogens in addition to four acid-fast bacterial species. None of these pathogens cross-reacted with either assay and so with initial specificity established, the assays were tested on non-tuberculosis mycobacteria (NTMs). The test data showed that the IS6110 assay cross-reacted with some mycobacteria that are not associated with the TB disease. *M. chimerae,* M. *nebraskense,* and *M. scrofulaceum* are related species when examined by spoligo typing and all cross-reacted with the IS6110 assay. No NTMs tested cross-reacted with the IS1081 assay.

The final component of the RPA assay evaluations was to test them on sputum samples derived from patients suspected of having TB. The IS6110 assay was tested on a total of 79 isolates. In the first pass, a total of 22/33 +ves were identified correctly by RPA and 44/46 mycobacterium tuberculosis complex (MTBC) –ves were identified correctly. Because 11 of the true positives were scored as –ves, we decreased the sample volume. This retesting produced 5 positive reactions and 6 remained negative. Contamination was suspected or the presence of an NTM that was reactive with the IS6110 assay. With the IS1081 assay, 71 specimens were tested, some of which were the same as used in the IS6110 experiment and some were different. The IS1081 identified 32/35 MTBC correctly as +ves and 35/36 correctly as –ves.

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 worked to develop a fluorescent detection system for strip tests to improve test sensitivity. We developed a europium latex conjugate that can be excited using a simple ultraviolet (UV) light source and emits in the visible spectrum. We also worked to develop and evaluate a simple, handheld reader for this fluorescent approach that combines inexpensive charge-coupled 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 improved the sensitivity of the strip test 160 times over the level of detection we observed with a standard colloidal gold system.

PATH evaluated the underlying technologies for the handheld device against commercially available bench-top analyzers. We conducted research and development of the strip, specifically focusing on technologies for immobilizing and rehydrating conjugated europium beads in the lateral flow test strip. A market research assessment was conducted to better understand the need and market for reader-based strip tests. Based on our findings and the relative performance of the prototype test system to other commercially available systems, work on this project has been concluded. In the future we hope to apply the knowledge gained with conjugation and stabilization chemistries and methods as well as europium bead detection to other diagnostic test systems which may use europium particles as part of the platform.

Microscopic observed drug susceptibility testing for tuberculosis

Cayetano Heredia University Peru, Hardy Diagnostics, PATH, and Wellcome Trust/London School of Hygiene and Tropical Medicine are developing an all-in-one kit for carrying out microscopically observed drug susceptibility (MODS) testing for multi-drug-resistant tuberculosis (MDR TB). TB grows more quickly in liquid than solid culture, and the collaborators from Peru and the United Kingdom developed a “home brew” MODS method for more rapid MDR TB determination. PATH joined the consortium to standardize the assay and to identify and partner with a manufacturer who could put all assay reagents/components into a single “kit.” Hardy Diagnostics and PATH have developed such a kit and are currently evaluating its performance in Peru and United States populations.

A recent evaluation in Peru (N=215 patients) showed strong concordance with standard home brew MODS and with gold standard testing methods. We are currently developing a protocol for a pivotal study for Peru regulatory approval. Follow-on activities will include prospective evaluations in other sentinel countries in Africa and South Asia. Additionally, the technology transfer is complete, and Hardy Diagnostics is currently selling kits for research purposes.

Immunization

Fast-dissolving tablets for oral immunization

Formulating live attenuated vaccines, particularly those for oral delivery to infants, is technically challenging in terms of manufacturability, the degree of stability improvement, and procedures necessitated by preparing the formulation at the time of use. Temperature stabilization, in particular, has been a challenge for live attenuated enteric vaccines.

In this project PATH and Oregon Freeze Dry, Inc., investigated the fast-dissolving tablet (FDT) in a blister package as a platform technology for formulating oral vaccines. The experiments were conducted using a live attenuated *Escherichia coli* strain—ACAM 2027, a component of the trivalent ACE 527 vaccine under development to prevent diarrheal disease caused by enterotoxigenic *E. coli* (ETEC) in at-risk travelers and pediatric populations in ETEC-endemic areas of the developing world. The liquid formulations evaluated—consisting of carefully selected buffers, ionic salts, stabilizers, bulking agents, and binders—were prepared, dispensed into preformed blisters, frozen, and lyophilized using a standard lyophilizer. The blisters were heat sealed and the formulations were evaluated for tablet properties and viability of bacteria. Following several rounds of experiments, a lead FDT formulation was identified. The tablets had excellent handling ability, disintegrated in less than 10 seconds, preserved the viability of the bacteria during the lyophilization process, and stored at refrigerated conditions (2^{o}C to 10^{o}C) for at least six months. This study indicates that the FDT in a blister package, produced using judiciously selected formulations and lyophilization cycles, is a viable option for formulating oral vaccines.

FDT formulation could potentially be administered to children directly as a tablet or as reconstituted liquid. This technology also appears robust enough to be used easily in adult subjects, such as travelers going to areas were the risk of infection with enteric and other mucosal pathogens is high. The FDT formulation offers the advantages of higher manufacture throughput at lower parenteral costs, ease-of-use presentation, and an effective temperature storage profile, and facilitates the formulation of multivalent vaccines. The compact size also allows for easy storage and distribution.

Since completion of the initial project in December 2010, the team has received funding from the Enteric Vaccine Initiative and Global Alliance for Livestock Veterinary Medicines to apply the technology to an ETEC vaccine and a Newcastle disease vaccine.

Performance and safety study of the PATH intradermal adapter

The PATH intradermal (ID) adapter is a low-cost injection aid designed to assist health workers give ID injections. ID injections are used to deliver BCG and anti-rabies vaccinations and tuberculosis testing, and could potentially be used for other vaccines. An ID injection uses approximately 80 percent less vaccine than a subcutaneous or intramuscular injection but can achieve the same or better immune response—an effect of particular interest to resource-strained immunization programs and vaccine manufacturers in developing countries. Because the traditional method of giving an ID injection can be difficult for some clinicians, ID injections for rabies vaccine has not been widely adopted even when data and cost savings vouch for their use. The PATH ID adapter is a simple approach to overcoming adoption hurdles such as specialized training and lack of practice. A preliminary clinical study, building on positive preclinical and bench testing, will demonstrate the performance and safety of the ID adapter. Visual observations and ultrasound will confirm the delivery of saline to the correct layers of skin in human volunteers.

A clinical trial protocol has been developed and approval has been received from PATH's Research Ethics Committee. Preparations are underway to conduct the study with a research organization in the greater Seattle area. This study is expected to begin in the second quarter of 2011. The results of this study will pave the way for future research with the ID adapter and vaccines in developing countries.

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 studied 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 an extended period of time to maximize the chances of the vaccine entering the tissue and subsequently providing an immune response. The formulation can be applied easily with a dropper or a sprayer. The formulation also contains a potent and safe mucosal adjuvant which augments the efficacy of the vaccine.

PATH's team in collaboration with Dr. Rodney Ho at the University of Washington and Dr. Edward Oaks at the Walter Reed Army Institute of Research,identified several lead formulations. Sublingual immunization of mice with thermosensitive gel (TRG)-formulated tetanus toxoid elicited high levels of secretory IgA antibodies to tetanus toxoid in saliva, the gastrointestinal tract, and the reproductive tract. The serum antibody level was almost identical to that elicited by intramuscular injection. However, imtramuscular injection of tetanus toxoid did not elicit mucosal antibodies. Several other formulations did not work. Similar findings were made with a *Shigella* vaccine, although the benefits of TRG formulation over the dmLT were not apparent in the immunogenicity of the *Shigella* vaccine. Our interpretation is that these mice were anesthetized during immunization, and retention time between the saline formulation and the TRG formulation was comparable.

TRG formulations may facilitate developing vaccines against many infectious diseases which are caused by pathogens spread by aerosol, contaminated water, food, or body fluids. This includes a handful of deadly diseases, namely diarrhea, HIV/AIDS, measles, pneumonia, and tuberculosis. The TRG formulation represents a novel and a potentially enabling technology platform for mucosal immunization.

The TRG formulations are easy to manufacture and use. Vaccine producers are familiar with manufacturing liquid formulations packaged in a dropper (e.g., oral polio vaccine) or a sprayer (e.g., FluMist®) device. Oral mucosal immunization using TRG formulations is needle free and amenable for self-administration.

Maternal and Neonatal

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.

The Child Health Research Foundation, based at Dhaka Shishu Hospital in Bangladesh, PATH, and the University of Toronto met to discuss the utility of biomarkers and approaches to improve diagnosis of severe infections among neonates. The outcome of this meeting was the creation of a strategy for specimen collection and biomarker assessment in a prospective study of neonates in four hospitals throughout the country. We will also comprehensively assess the literature and make a short list of biomarkers and their relevant gold standard diagnostic assays for use in an evaluation study.

Hemostatic agents for postpartum hemorrhage prevention

Hemostatic agents have gained widespread use for pelvic surgery in the last few years. Specifically, they excel for use in areas of difficult accessibility. PATH conducted research into the efficacy of hemostatic use for postpartum hemorrhage (PPH) management. The goal of this work is to establish the feasibility of scaled use of hemostatic agents and to identify appropriate delivery strategies for hemostatic agents as a PPH intervention. PATH continues to increase stakeholder awareness of the potential for the use of hemostatic agents for PPH treatment. We presented a technical update on haemostatic agents at the Challenges and Innovations in Handling Postpartum Hemorrhage Seminar, January 25, 2011, in Washington, DC, and we are seeking collaborators and funding to continue research in this high-impact area.

Infusion system

The goal of this project is to develop a non-instrumented ambulatory infusion pump for outpatient antibiotic therapy. Our team has developed a product profile and a product requirements specification for an intravenous (IV) infusion pump to treat osteomyelitis. Additionally, we developed a prototype and are currently bench testing a platform technology that consists of two electricity-free pumps connected to a peripherally inserted central catheter line through a "T." One branch for anti-fouling uses a low-rate infusor pump while the other line uses a higher-rate bolus pump to deliver a quick dose. While the current application is osteomyelitis, we are exploring the potential to use this platform technology for a wide variety of low-resource setting uses including outpatient antibiotic therapy and IV anesthesia delivery.

Nifty cup

Infants unable to breastfeed require a viable feeding option. Feeding devices in high-resource settings such as nasogastric tubes, bottles, and breast pumps are impractical and unhygienic in settings lacking clean water and electricity. For these reasons, the World Health Organization and the United Nations Children's Fund recommend hand expression of breast milk and the use of a small cup to feed these newborns. Conventional cups are often made of hard plastic that can cut a neonate's mouth, increasing infection risk. Physiologically cup feeding only requires the infant be able to swallow and breathe, which demands less energy and skill than the more complex and coordinated suck, swallow, and breathe mechanism needed for breastfeeding. Preterm infants and neonates developing this mechanism or fighting infection require supplemental short-term cup feeding until they can exclusively breastfeed. Infants with a cleft palate are unable to generate suction and require long-term cup feeding. For these infants, cup feeding of hand expressed breast milk confers immediate infection protection and provides long-lasting immunological, developmental, and psychosocial benefits. Motherless neonates and those born to HIV-positive mothers not on antiretrovirals require long-term cup feeding of breast milk from a wet nurse or formula. For these infants, consistent, sufficient intake at each feed in early life is critical for long-term health.

Our team will design and test the Neonatal Intuitive Feeding TechnologY (NIFTY) cup: a simple-to-use, easy-to-clean, low-cost device for the highly efficient delivery of expressed breast milk (or formula) to preterm and low-birth-weight newborns, infants born to HIV-positive mothers, motherless neonates, infants with orofacial clefts, and others unable to breastfeed. We hypothesize that NIFTY cup will be preferable to and more effective than conventional cup feeding used in low-resource settings. PATH has received matching funds from the University of Washington dental school to pursue this project. To-date, we have designed various cup prototypes, identified affordable and appropriate prototype manufacturers, and designed a user feedback evaluation on various prototypes with mothers in the Seattle area.

Noninvasive hemoglobin monitoring

Effective screening programs for iron deficiency anemia, especially for at-risk pregnant women and children, have been hampered by the lack of a simple, safe, and accurate lower-cost hemoglobin testing tool. Attempts to develop noninvasive anemia screening devices have been ongoing for many years. A noninvasive device that can be shown to be reliable, robust, and affordable would address a great need by expanding easy access to screening for iron deficiency anemia among high-risk populations—providing evidence to support early treatment— and facilitating population surveillance and monitoring efforts in low-resource settings. PATH identified two promising technologies that meet many of the required and desired specifications of an effective noninvasive device. These two noninvasive hemoglobin screening devices, the Pronto and the Pronto 7, were developed by Masimo Corporation (Irvine, CA), and build on their SET pulse oximetry technology. Both devices are United States Food and Drug Administration approved and are currently being used in developed countries. At present, PATH and Masimo are identifying field evaluation opportunities in low-resource settings, and we are discussing Masimo's interest in market development and business model innovations.

ORS tablets

Despite its proven effectiveness, knowledge about and use of oral rehydration solution (ORS) has stagnated in many countries and is declining in others. Negative perceptions by consumers and providers persist about ORS including its inability to treat illness and address the symptoms of diarrhea, its perceived inferiority to antibiotics and drugs as treatment, and challenges with preparation and administration. Developing a new presentation of ORS has the potential to stimulate the current market and increase uptake and use of this proven, low-cost intervention. To that end, PATH is exploring the feasibility of an ORS tablet to improve consumer satisfaction and increase demand.

In 2010, PATH collaborated with CoreRx to produce prototype ORS tablets using the current World Health Organization (WHO) low-osmolarity formulation of ORS. The result is a split-tablet presentation with one tablet equal to a current ORS 200-ml sachet (five tablets required for one liter). PATH met with stakeholders at WHO, showed the prototypes, and received positive encouragement to move forward with the project. Next steps for the project are to optimize the tablet, detail manufacturing scenarios and market readiness, and document end-user perspectives and health system fit for this new presentation.

Perinatal Intervention Package 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, antenatal corticosteriods, and emerging lung support technologies for use in lower-resource settings can improve outcomes for preterm infants. PATH, in collaboration with the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS), is exploring the feasibility of the Perinatal Intervention Package. To date, the team has used the summary from the GAPPS 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.

Identification of essential equipment for each resource level and behavioral change communication required for specific levels of care is underway. However, optimal operational pathways for lowest-resource settings still need to be determined. Testing the acceptability and feasibility of the Perinatal Intervention Package in a mid-level resource setting will be critical to demonstrate the usefulness of this approach. Team members conducted stakeholder/provider interviews in one district-level facility in Uganda as part of a regularly scheduled technical assistance visit. Results from these interviews identified that this approach would be helpful and feasible in such a setting and raised a variety of issues related to implementation of the package of care. A more rigorous collection of feedback from stakeholders at all

levels of health service delivery (tertiary, district, primary, and community) on the feasibility of algorithms and corollary equipment needs in each setting is needed. Once feedback is obtained from all sources, a more detailed paper that describes current best practices, gaps in practice, and commercial availability of equipment for each specific intervention as they relate to each delivery care setting may be produced.

Other

Clean cookstoves

The goals of the clean cookstoves project are to allow PATH to actively engage in the rapidly growing global dialogue on clean cookstoves and to seek funding to contribute to reducing indoor air pollution through the effective introduction of improved cookstoves.

PATH participated in the Global Alliance for Clean Cookstoves (GACC), a ten-year, US$250 million private/public partnership of nongovernment organizations, governments, United Nations agencies, and the private sector all working on aspects of advancing the clean cookstove agenda. We are members of both the Monitoring and Evaluation (M&E) Working Group and the Health Working Group of the GACC. The mandate for the M&E Working Group is to make recommendations for the development and implementation of an effective M&E system that covers achievements of the GACC's target of adoption of 100 million cookstoves by 2020. PATH is serving as the coordinator for the M&E sub-group on impact. An outcome of participation on the GACC is direct connection to many global cookstove experts, which will aid in identifying the best use of PATH's skills. As a result of this project, the team has increased its depth of knowledge on cookstoves and has formed linkages with other groups such as Burn Design Labs in Vashon, WA, and Ahuyu, which was founded by Dr. Justin Schram, an internal medicine resident at the University of Washington.

Emergency contraception as a pericoital contraceptive

The goal of this project is to assess the feasibility of repositioning the existing levonorgestrel (LNG) formulation of emergency contraception (EC) as a pericoital method of contraception (pill taken soon before or after intercourse). Recent reviews of EC have helped reframe the possibility of using EC as a regular method for women who have infrequent intercourse. A pericoital method of oral contraception could provide women with several advantages not offered by existing methods, including reduced dosing frequency, convenience and privacy, and greater likelihood of dosing adherence given pill use would not be daily, but rather tied to a coital act. Specifically, PATH's objective is to provide stakeholders (partners in the International Consortium for Emergency Contraception [ICEC] and donors) with information that can guide strategic thinking about developing and introducing a pericoital method. We aim to develop a critical pathway that will illustrate key decision points and activities for comprehensive introduction of a new, dedicated pericoital contraceptive product.

Our initial review of available published literature on this topic helped inform the decision to focus more substantial resources on discussions with expert stakeholders to gather new information on clinical feasibility and potential demand, which informed the development of a critical pathway. Between January and March, we conducted 35 discussions with more than 40 representatives of donors and peer organizations, including those working at both international and national levels, as well as several representatives of pharmaceutical manufacturers of LNG. Based on analysis of the data, we will revise the critical pathway developed at the outset of the project and draft a report that includes specific recommendations of steps forward. The pathway and narrative will be broadly disseminated to interested stakeholders starting with ICEC members and including public-sector groups, colleague organizations, pharmaceutical manufacturers and distributors, and donors.

PATH may receive a sub-award from Gynuity Health Projects to plan for introduction of this method and conduct demand/pricing assessments in two countries. This will position us to continue work to support development and introduction, should the results of the Phase 3 clinical trials be sufficient to secure regulatory approval for the method.