HealthTech

Technologies for Health

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By

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Executive Summary

For the past 24 years, PATH has been developing, adapting, transferring, and introducing appropriate new health technologies for resource-poor populations. In 1987, USAID started funding PATH's work in this area through a cooperative agreement with PATH called the Technologies for Child Health: HealthTech program. This agreement was renewed in 1990 and then again in 1996 as the Technologies for Health program (HealthTech III). This report primarily summarizes the activities under the program during the last agreement, but also reflects work under the entire term of HealthTech since so much of the work is a continuum.

The primary goal of HealthTech has been to identify health needs that can be met with technology solutions, and then either identify existing technologies that need adapting to be affordable and appropriate, or develop new ones. This research and development phase includes design, development, scale-up, evaluation in the laboratory and field settings, and finally introduction of technologies for health, nutrition, and family planning. Over the last ten years, HealthTech has effectively scaled up these activities and developed a critical mass of in-house expertise in product and diagnostic design, engineering, evaluation, and introduction of developing world technologies. Multiple collaborations with private industry and global and local agencies and nongovernmental organizations (NGOs) have been established. Under HealthTech and other similar programs, PATH to date has worked with 57 private-sector companies (21 U.S. firms, 14 additional industrial-world firms and 22 developing-world firms) and at least 40 public-sector partners (22 in the developed world and 18 in developing countries). The results of these collaborations have been to advance more than 30 economically sustainable technologies—17 of which are now in use in more than 25 developing countries. Six of these products are currently being (or have been) distributed worldwide by global agencies.

A key tenet, and the major challenge of this program, has been to make appropriate technologies available to developing-country programs in ways that can become economically sustainable, independent of continuing donor support. To do this, HealthTech has fostered both collaboration and coinvestment. HealthTech has also brokered successful partnerships between industrial-world and developing-world firms; facilitated south-to-south collaboration for the introduction of new priority products; and built local capacity for total quality management, research and development, procurement, and marketing. HealthTech functions as a value-adding, technical program and, as such, has built trust and developed extensive networks including large and small health-product firms, World Health Organization (WHO), United Nations Children's Fund (UNICEF), United Nations Population Fund (UNFPA), bilateral agencies and governments, NGOs throughout the developing world, as well as many USAID cooperating agencies. PATH has leveraged public-sector resources by creating valuable intellectual property and by defining markets and introduction strategies which attract commercial coinvestors. Ultimately, all technologies are transferred to carefully selected industrial collaborators (licensees or codevelopers) for scale-up, manufacturing, and marketing, both in developed and developing countries. The investments that these companies make in the products have been significant.

I. Accomplishments Under HealthTech III

Working closely with USAID to meet their strategic objectives, HealthTech has advanced and introduced the following representative technologies during the past three years. (More detailed information on specific technologies appears in the next section of this report). The outcomes of technology introduction can be seen in the impact on policy, supply systems, and health programs, as shown in the examples that follow:

Strategic Objective #1: Increased use by women and men of voluntary practices that contribute to reduced fertility.

- **Uniject™ prefill injection device for use with injectable contraceptives**
  HealthTech has negotiated with injectable contraceptive manufacturers to conduct required stability testing on their products filled into the Uniject device. PATH provided technical assistance to a Mexican manufacturer of Cyclofem® injectable contraceptive in Uniject devices.

- **Autodisable (AD) syringes for injectable contraception**
  HealthTech has assisted USAID with introduction of AD syringes to reproductive health cooperating agencies by drafting specifications of syringes and safety boxes for USAID procurement and by providing a generic training manual on safe injection.

Strategic Objective #2: Increased use of key maternal health and nutrition interventions.

- **Oxytocin in Uniject devices**
  HealthTech designed and developed the Uniject device now manufactured by BD. HealthTech worked with a private company to fill the device with oxytocin, evaluated its use by midwives in Indonesia in delivering at-home doses of the medicament to prevent hemorrhage at birth, and collaborated with WHO on the evaluation in a developing country.

- **AD syringes and other safe-injection devices to more cost-effectively and safely deliver tetanus toxoid (TT) to women**
  TT in Uniject devices is being provided under the Partnership for Child Health program sponsored by UNICEF. For this program, 9 million Uniject devices have been donated by BD, 9 million doses of tetanus toxoid by P.T. Bio Farma, and 9 million Vaccine Vial Monitors (VVMs) by LifeLines Technologies, for use in UNICEF's TT elimination program.

- **Syphilis diagnostics**
  HealthTech codeveloped, optimized, and validated a simple, rapid test for diagnosis of syphilis; and licensed the original test to a private-sector manufacturer. HealthTech developed and validated a second immunochromatographic strip (ICS) test based on an alternative antigen. This rapid syphilis test was evaluated in Mexico and Peru. A generic global introduction strategy for all rapid syphilis tests is being developed and will be launched.

- **Safe-birth delivery kits to reduce the incidence of tetanus among women and newborns**
  HealthTech provided technical assistance to NGOs in Nepal to develop a locally appropriate and locally produced kit, which received highest government approval. The kit was later

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Uniject™ is a trademark of BD.
Cyclofem® is a registered trademark of The Concept Foundation.

evaluated in a quantitative study to determine the impact of use of the kits on cord infection, which correlated positively. Workshops were conducted in India and Africa for NGOs to assist them in starting delivery kit projects. A comprehensive guide to developing local delivery kit programs was developed and is being distributed.

- **Anemia detection methods**
  HealthTech developed, assessed, and introduced an improved visual scale to detect anemia, and assisted WHO in assessing manufacturing strategies. Two manuals were published for dissemination–*Anemia Detection in Health Services: Guidelines for Program Managers* (translated also into French and Spanish), and *A Manual for Health Workers–Anemia Detection Methods in Low-Resource Settings*.

Strategic Objective #3: Increased use of key child health and nutrition interventions.

- **Vaccine Vial Monitors (VVMs) to improve vaccine management**
  VVMs, indicators of cumulative heat for vaccine vials, were developed to respond to the need to reduce vaccine wastage and increase immunization effectiveness. Now, VVMs are specified on all vaccines to be purchased by UNICEF from 2001 to 2003, including new vaccines purchased by the Global Fund. From 1996 to 1999, 326 million VVMs were distributed with oral polio vaccine (OPV); the commercial collaborator estimated that in year 2000, 122 million VVM units on a variety of vaccines were distributed; and at least 8 vaccine manufacturers are now using VVMs. VVMs have influenced change in the WHO multi-dose vial policy, and were added as an extension to all UNICEF-procured vaccines starting in 2001. All Global Alliance for Vaccines and Immunization (GAVI) Global Fund vaccines must now have VVMs. National vaccine manufacturers in four developing countries are using VVMs. Training materials for EPI workers on VVMs were developed as part of a global introduction strategy. HealthTech also assisted Serum Institute of India to pioneer application of VVMs to the removable lid of measles vaccine vials.

- **Uniject device to increase immunization coverage**
  The Uniject device was licensed to BD, a large, multinational pharmaceutical company with worldwide distribution capabilities. Six vaccine/pharmaceutical manufacturers are conducting preregistration activities to use Uniject devices. HealthTech helped establish P.T. Bio Farma in Indonesia as a primary producer of TT and hepatitis B vaccine in Uniject devices. Through the USAID/New Delhi Program for Advancement of Commercial Technology-Child and Reproductive Health (PACT-CRH) program, HealthTech worked with two manufacturers in India to develop capacity to fill Uniject devices with hepatitis B vaccine.

- **AD syringes for use in Expanded Program on Immunization**
  PATH designed, developed, and validated the first mass-produced, autodisable syringe (SoloShot™) and then helped design a two-piece version of the SoloShot AD syringe available made at a lower cost. SoloShot AD syringes are in widespread use in immunization programs throughout the developing world. They are incorporated to increase safe injection practices for both routine immunizations and in mass immunization campaigns. Since commercial introduction in 1992, more than 400 million SoloShot AD syringes have been supplied to public health programs in over 40 developing countries in Africa, Asia, Eastern Europe, and Latin America.

Soloshot™ is a trademark of BD.

- **Determinations of vitamin A levels**
  HealthTech developed and validated the retinol binding protein enzyme immunoassay (RBP-EIA) for use in identifying vitamin A deficiency among populations. The test was evaluated in three countries, laboratory validation study results were presented at the International Vitamin A Consultative Group meeting in February 2001, and HealthTech is currently negotiating with private-sector manufacturer for licensing and technology transfer.

- **Needle-removal concepts to improve medical waste disposal**
  HealthTech has analyzed key barriers, investigated scenarios of use, interviewed and invited input from policy makers and safety experts; assessed local needs and practices, evaluated electrical needle-destroyers, and developed draft specifications for WHO. Recently HealthTech has designed and developed two needle-removal technologies, and is currently conducting design-stage field trials in India.

- **Safe injection activities**
  During the course of developing various injection devices and immunization-related technologies under HealthTech, PATH has developed in-depth knowledge of safe injection and immunization practices. Among the activities that HealthTech has undertaken because of this technical expertise are: assistance with design and development of a WHO web site on injection safety; involvement in the founding, development, and facilitation of the Safe Injection Global Network; development of a training manual called *Giving Safe Injections: Using Auto-Disable Syringes for Immunization*; and provision of training materials, curriculums and trainers on safe injection to WHO/EPI programs.

Strategic Objective #4: Increased use of improved, effective, and sustainable responses to reduce human immunodeficiency virus (HIV) transmission and mitigate the impact of the HIV/AIDS pandemic.

- **HIV dipstick**
  The HIV dipstick is a very low-cost, simple HIV test developed by PATH that is currently being produced by four manufacturers located in the developing world. During HealthTech III, technical support was provided to several manufacturers to improve the quality of their tests. Recently, an evaluation of where and how the HIV dipstick is currently being used indicates that it is the lowest-priced HIV test on the market and has a specific market niche in the public and private sectors of Asia, Latin America, and Africa. Between 1993 and 1999 a total of 5.2 million tests were sold internationally.

- **Syphilis diagnostics**
  A simple, rapid ICS syphilis test was developed by HealthTech and transferred to two producers. HealthTech has performed clinical evaluations of several rapid syphilis tests in Peru and Mexico and presented this data at the International Society for STD Researchers conference in June 2001. HealthTech is actively involved in efforts to promote the introduction and appropriate use of all rapid syphilis tests. HealthTech is working with WHO and the STD Diagnostics Initiative to develop a consensus document on the laboratory methods for evaluation of rapid syphilis tests.

- **Gonorrhea and chlamydia diagnostics**
  Working in collaboration with a private sector firm, HealthTech has established proof of concept for rapid, low-cost ICS tests for gonorrhea and chlamydia. HealthTech is currently validating the tests on samples from different populations.

Strategic Objective #5: Increased use of effective interventions to reduce the threat of infectious diseases of major public health importance.

- **Diagnostics for malaria**
  HealthTech has developed and validated a rapid, low-cost ICS version of the malaria test and conducted field evaluations in Peru and Malawi. HealthTech transferred the technology to producers in Canada and India and is currently in negotiations with a third producer. HealthTech also assisted several commercial producers to facilitate their malaria test development and convened a workshop with USAID and others in the field to determine appropriate specifications for malaria diagnostic tests; and to develop introduction strategies for all rapid malaria tests. A decision tool for program managers was developed to help them choose the appropriate malaria test for their particular situation.

- **Tuberculosis (TB) diagnostics**
  HealthTech is currently developing a simple, rapid ICS test for the diagnosis of active TB infection. It has been validated in the laboratory and PATH is conducting field evaluations.

II. Skunkworks/Predevelopment Activities

During the course of HealthTech III, a portion of the budget was set aside for PATH to conduct feasibility assessments of promising technologies prior to USAID approval as full work plans. The "predevelopment fund" or "skunkworks" generally supported $10,000 to $20,000 worth of investigative work, without incurring significant investments or commitments. This predevelopment analysis usually concentrated on the technical feasibility of a technology and whether it adequately would solve the identified health need. Other foci of the analysis were often cost effectiveness of the product, the availability of commercial partners, and the market feasibility, but usually a technology was moved to a full work plan before an analysis of these factors was undertaken.

From 1996 to 2001, HealthTech used the funds for a total of 34 predevelopment projects. Of these, a total of 12 were converted to full project status, either under HealthTech or other programs. These included the anemia detection device, Uniject device with gentamicin, vitamin A diagnostic, tuberculosis test, diptheria test, Ultra Rice™, oral polio vaccine dropper, vaccine reconstitution devices, vaccine preservation technologies, vaccine cool boxes, commercial cold chain methodologies, and a manual on safe injection. Among the technologies which were considered but not advanced for various reasons were: measles timer, dry vaccine injection approaches, waste incinerator, deet bar soap, shigella diagnostic, hepatitis C diagnostic, ozone sterilization, screening devices for drugs, *Haemophilus influenzae* type b (HIB) diagnostic, streptococcus diagnostic, BCTP decontaminant, newborn resuscitator, and *H. ducreyi* test. Some of the funds were also used to establish web sites–HealthTech provided technical assistance in designing and developing a safe injection web site for WHO and HealthTech has developed its own web site on rapid, low cost tests for infectious diseases.

III. Report of Individual HealthTech Projects

The following pages contain individual reports for HealthTech projects.

Ultra Rice™ is a trademark of Bon Dente International.

Uniject Prefill Injection Device

Health Need Addressed

Recent surveys in developing countries have revealed that 30 to 50 percent of injections are not sterile. Disposable syringes are reused, and reusable syringes are often improperly sterilized. The risks of transmission of bloodborne pathogens such as hepatitis B and HIV are great. New methods are required to ensure that a sterile syringe is available for each injectable dose delivered.

HealthTech III Solution and Potential Impact

The Uniject device was developed during HealthTech I, II, and III and has been licensed to BD for commercial production. It is a prefilled, single-dose injection system specifically designed to prevent attempts at reuse. Uniject devices are available in 0.5 ml- and 1.0 ml-dose sizes and can be ordered with any standard-size needle.

Recent improvements in vaccine stability have resulted in the modification of rules for cold storage of some vaccines (e.g., tetanus toxoid and hepatitis B vaccine) thereby facilitating their delivery to hard-to-reach areas. The Uniject device is an ideal delivery mechanism for these vaccines, as well as for injectable contraceptives and emergency medicines such as uterotonic drugs for treatment of postpartum hemorrhage. This technology simplifies the act of giving an injection, makes the unsafe reuse of the syringe impossible, and reduces the burden on logistics systems by making premeasured medicament, needle, and syringe available at the same place and time. Uniject devices may be appropriate for use in the home or community by outreach workers who do not traditionally deliver injections.

Status of Technology in 1996

Invented at PATH with funding from HealthTech, the device was licensed to BD for production and distribution during the first year of HealthTech III. Prior to that, during the years of research and development, PATH worked with Horizon Medical, a medical packaging company.

Activities 1996-2001

- Published results of field trials of Uniject devices that had been successfully completed with Cyclofem injectable contraceptive in Brazil, tetanus toxoid (TT), and hepatitis B (HB) vaccine in Indonesia, and TT in Bolivia.
- Conducted trials with midwives in Indonesia using Uniject devices to deliver oxytocin to mothers giving birth at home to prevent postpartum hemorrhage.
- Worked closely with BioFarma, Indonesia's vaccine producer, in establishing filling capacity and in achieving WHO approval of Uniject devices.
- To establish competition and sufficient supply, PATH collaborated with three producers in India who are investigating the use of the Uniject device.
- GAVI offered HB-Uniject as an option (beginning in 2002) to countries receiving GAVI support.
- Worked with United Nations Children's Fund (UNICEF), BD, and others through the Partnership for Child Health to prepare to use TT-Uniject devices for tetanus elimination in priority countries beginning in 2002.

- The Bill and Melinda Gates Children's Vaccine Program's (CVP) introduced one million HB-Uniject devices for at-home neonatal immunization in three Indonesian provinces. This successful outreach project prompted the Indonesian government to procure an additional one million HB-Uniject devices in 2000 to 2001 for use in several other provinces.

Status of Technology in 2001

Seventeen companies have conducted pilot fills, and five have procured Uniject device filling lines. Commercially available products in the Uniject device include HB vaccine and TT from P.T. BioFarma (Indonesia), and Cyclofem from Aplicaciones Farmaceúticas (Mexico).

UNICEF and BD have instigated an initiative against tetanus through the Partnership for Child Health. Uniject devices will be used to deliver TT to women in remote populations throughout the world, beginning with Ghana and Mali in 2002. Vietnam and China are preparing to introduce HB-Uniject with support from GAVI.

Plans for the Future

Ideally the Uniject device will be the first of many self-contained, unit-dose administration systems to become available for developing country settings. The transition from multi-dose to unit-dose presentations has been part of the overall Expanded Programme on Immunization (EPI) vision for safe and efficient administration of vaccines for many years, and is compelled by the much higher cost per dose of newer vaccines and the need to remove mercury-containing thimerosol preservative from vaccines. Current Uniject device introduction efforts by PATH under HealthTech and other programs are therefore focused on assessing the cost/benefit of the device for specific applications, as well as monitoring and disseminating lessons learned.

Oxytocin in Uniject Devices

Health Need Addressed

Hemorrhage is the leading cause of maternal mortality and is a particular problem in home deliveries because the short response time makes referral impractical in most cases. The use of oxytocin for routine management of the third stage of labor can significantly reduce the incidence of postpartum hemorrhage. Active management of the third stage of labor, which includes routine use of a 10 IU dose of oxytocin given intramuscularly, is recommended by WHO for all institutional deliveries and home deliveries attended by a person with midwifery skills.[1]

HealthTech III Solution and Potential Impact

A prefilled, nonreusable syringe, such as Uniject, is thought to be the safest mechanism for delivering the life-saving benefits of oxytocin to women in peripheral health care settings and homes. This prefilled, injection-ready format ensures that an accurate dose is given in a nonreusable, sterile device with minimal preparation and minimum waste, making it ideal for use in emergency situations and remote locations.

Status of Technology in 1996

By 1996, validation and licensing of the Uniject device to BD was complete; PATH was starting to investigate all the various applications of the device, beyond immunization programs. Uniject devices had been filled with oxytocin by Gedeon Richter Ltd. in Hungary for stability testing; long-term and accelerated tests had shown good results (1995).

Activities 1996-2001

- Uniject devices filled with oxytocin by Aplicaciones Farmaceúticas (AF) in Mexico, using raw material provided by Gedeon Richter and formulated by AF, for stability testing and use in field evaluations by World Health Organization (WHO) and PATH/HealthTech (1998).
- Protocol for field evaluation in Angola developed by PATH/HealthTech in collaboration with WHO Safe Motherhood Programme and Karolinska Institute (1996-1998); 1,500 devices shipped to WHO for forwarding to Angola for start of trial in two clinic sites (1999).
- Field evaluation in Indonesia conducted in collaboration with WHO/Indonesia and the Indonesian Ministry of Health (1998-1999); 2,300 devices used for trial in Lombok among midwives doing home deliveries (1999).
- Identified potential oxytocin manufacturers in Indonesia, including Bio Farma, which already has the filling capacity for Uniject devices with vaccines.

Status of Technology in 2001

The field trial of oxytocin in Uniject in Indonesia showed widespread acceptability and interest in using Uniject for home delivery of oxytocin to birthing mothers. Midwives were able to use the

[1] *Mother-baby package: Implementing safe motherhood in countries.* WHO/FHE/MSM/94.11, Geneva, 1994.

device appropriately and effectively with only brief training and dispose of it safely. In addition to the added convenience, Uniject devices contributed to an improvement in dose accuracy and injection safety compared to reported baseline practices.

Plans for the Future

PATH plans to continue to facilitate interested oxytocin producers in working with BD to set up pilot filling lines for the production of devices until there is at least one supply source available in each major region. PATH will also organize introductory studies or pilot introduction programs in countries with need and interest, evaluate the cost-effectiveness of oxytocin in Uniject in comparison with alternate interventions, and carry out post-introduction surveillance to identify any logistical or other problems. PATH will also disseminate information about experiences with the product to raise awareness and enhance adoption (through publications and presentations at meetings).

Gentamicin in Uniject Devices

Health Need Addressed

The World Health Organization (WHO) estimates that at least 4 million neonatal deaths (i.e., death during the first 28 days of life) occur around the world every year. Severe bacterial infections are major contributors of newborn morbidity and mortality. Each year, an estimated 30 million children born in the developing world contract an infection during the neonatal period, and infectious diseases account for over one-third of all neonatal deaths. In 2000, a WHO advisory committee recommended intramuscular injections of ampicillin and gentamicin as the standard therapy for these bacterial infections and the treatment of neonatal septicemia, meningitis, and pneumonia. Case-fatality rates for severe bacterial infections are high in part due to not administering or to delaying the administration of necessary antibiotics. Therefore, it is important that newborns with these infections receive immediate treatment, even before the infectious agent is known. When neonatal infections occur, many deaths can be avoided if the signs are recognized early and the disease is treated promptly.

HealthTech III Solution and Potential Impact

Uniject injection devices prefilled with a single gentamicin dose (hereafter called "gentamicin-Uniject") could be easily transported and used in a home setting with an oral antibiotic, when the signs of a neonatal infection are first detected, to improve neonatal survival from infectious diseases. Community-based health workers could be trained to use gentamicin-Uniject and a complementary oral antibiotic in order to extend the accessibility and facilitate the administration of antibiotics for early treatment of neonatal infections. Furthermore, gentamicin-Uniject could potentially be incorporated into the revised integrated management of childhood illness (IMCI) guidelines, which have been adapted for acute management of common infectious, neonatal, illnesses. If gentamicin-Uniject is used safely, properly, and efficiently for infants with severe bacterial infections, then Uniject devices may make a significant contribution to reducing neonatal mortality in developing countries.

Status of Technology in 1996

This application for the Uniject device was visualized in 1996, but HealthTech activities at that time were focused on development of Uniject devices for use with vaccines and injectable contraceptives.

Activities 1996-2001

Preliminary planning regarding the feasibility of filling gentamicin-Uniject devices and conducting compatibility testing has been initiated with a pharmaceutical manufacturer in Mexico. Discussions with various users in the field have verified that gentamicin-Uniject would provide an innovative and potentially important method of treating neonatal sepsis and reducing its harmful effects.

Status of Technology in 2001

Bulk gentamicin has been delivered to the pharmaceutical manufacturer in Mexico; their agreement to initiate compatibility testing is being finalized. The identification of a consultant that can perform a pharmacokinetic analysis of appropriate pediatric dosage formulations is underway. A proposal has been submitted to Save the Children's Saving Newborn Lives initiative to incorporate field evaluation activities of gentamicin-Uniject within existing research studies in Bangladesh and/or Pakistan.

Introduction of Injectable Contraceptives in the Uniject Device

Health Need Addressed

Injectable contraceptives are becoming increasingly popular around the globe as women search for safe, highly effective, reversible methods of contraception that do not require compliance with a daily regimen. Depot medroxyprogesterone acetate (DMPA) is administered by injection once every three months, making it highly convenient. Cyclofem injectable contraceptive is administered by injection every month and is formulated to allow women to have more normal menstrual cycles—an advantage in many cultures. Currently, international development and family planning agencies purchase over 25 million doses of DMPA injectable contraceptives annually for distribution to family planning programs throughout developing countries. Approximately 7 million doses of Cyclofem injectable contraceptives were sold in the year 2000.

International development and family planning agencies and recipient governments are continually looking for feasible and affordable methods to reduce unsafe injection practices that could lead to the spread of bloodborne diseases. Provision of one sterile needle and syringe with every dose of injectable contraceptives is the current standard. However, there is a risk with disposable syringes that they will be reused. AD syringes prevent reuse, but like disposable syringes, they can be diverted to other uses during the distribution process. The Uniject device has distinct advantages in terms of both safety and procurement.

HealthTech III Solution and Potential Impact

A decade ago, prefilled syringes were too costly for use in public-sector health programs, and no prefilled syringe on the market offered an AD feature. Under the HealthTech project, PATH was able to develop the Uniject device, a proprietary, prefilled, AD injection system. The Uniject device prevents reuse, simplifies matching of syringes and supplies, ensures dose accuracy, and is so simple to use that injection at home by the patient or a family member is feasible.

Status of Technology in 1996

By 1996, validation and licensing of the Uniject device to BD was complete, and PATH was starting to investigate a variety of public health applications for this injection system. The Office of Population was particularly interested in having PATH investigate the possibility that Uniject could provide an easy, affordable, and self-administration method of delivering injectable contraceptives.

Activities 1996-2001

DMPA in Uniject Devices

- A formal solicitation and competitive selection process was used by PATH to encourage pharmaceutical candidates to pursue this product combination. Pharmacia & Upjohn (P&U) New Jersey, was chosen (1998).
- DMPA was filled into Uniject devices for initial compatibility studies at P&U's facility in Belgium using temporary filling equipment. The six-month results of this study, suggested that changes in either the DMPA formulation or the approach for pouching the Uniject device were necessary to address a pH shift that occurred during storage (1998–1999).

- Pharmacia (name changed from Pharmacia & Upjohn) initiated development of a revised formulation of their DMPA to enhance, among other things, potential compatibility with the Uniject device (2000).
- USAID Office of Population decided to bundle AD syringes and sharps disposal containers with DMPA as an interim solution until DMPA-Uniject is available. PATH developed training materials and assisted with introduction of the concept among cooperating agencies (CAs) (2000–2001).
- Pharmacia filled the revised DMPA formulation into Uniject devices for a second compatibility study and has expressed high confidence in achieving satisfactory results (2001).

Cyclofem Injectable Contraceptive in Uniject Devices

- PATH provided ongoing technical support and relationship facilitation between BD and the Mexican producer of Cyclofem injectable contraceptive, Applicaciones Farmacueticas (AF), as AF developed production scale capacity to produce Cyclofem-Uniject (1997–2001).
- Due to unforeseen regulatory delays in 2000–2001, AF has not yet launched the sales of Cyclofem-Uniject in either the private or public sector in Mexico.

Status of Technology in 2001

BD produces empty Uniject devices in their plant in Singapore at a production capacity of 250 million units per year. Pharmacia has now completed its DMPA product reformulation and undertaken a second round of compatibility testing for Uniject devices. Pharmacia expects to have preliminary compatibility data on the reformulated DMPA-Uniject in December 2001. PATH/HealthTech will facilitate a meeting of all parties (USAID, PATH, BD, Pharmacia) to review the preliminary compatibility data and establish timing and responsibility for the steps to follow in the development, regulatory, and introduction process. PATH will also continue to assist USAID with autodisable syringe and sharps disposal container introduction, as needed.

PATH is continuing its relationship with AF which developed a version of its one-a-month injectable contraceptive, Cyclofem, in Uniject devices. Pharmacia also is now marketing their version of Cyclofem, called Lunelle™, and is conducting preliminary compatibility studies with Lunelle in Uniject devices. PATH will maintain contact with both companies to look for opportunities for introduction.

Plans for the Future

After the meetings with Pharmacia, BD, and USAID in December 2001, PATH will shift focus from development to early stage introduction planning and support with USAID Office of Population and its primary contraceptive service delivery CAs. This shift is dependent on resolving the compatibility issues of DMPA in the Uniject device, and Pharmacia making a firm commitment to move forward with USFDA approval.

Lunelle™ is a trademark of Pharmacia.

Vaccine Vial Monitors

Health Need Addressed

Vaccines must be protected from excessive heat exposure during storage and transport to the point of use, or they may not provide sufficient immunity to the children who receive them. Appropriate temperature storage is difficult to maintain as vaccine is transported from the manufacturer to the recipient via the cold chain. In the past, health workers had no way to verify whether vaccine was potent or useless, since vaccine does not change appearance when it degrades. As a result, immunization programs have adopted conservative guidelines for vaccine handling and disposal of vaccines when heat exposure is suspected. This often results in disposal of good vaccine—by programs where resources are already scarce.

HealthTech III Solution and Potential Impact

VVMs are small, circular indicators that are printed directly on vial labels or adhered to the tops of vials, ampoules, or tubes. The inner square of the VVM changes color irreversibly from light to dark with exposure to heat over time. By comparing the color of the inner square to the surrounding reference color, a health worker can determine the extent to which the vaccine has been exposed to heat. VVMs provide health workers with a clear warning when vaccine should be discarded. At minimum, they allow health workers to prevent delivery of heat-damaged vaccine and reduce the discard of usable vaccine. There are also more sophisticated and revolutionary uses for VVMs.

Polio eradication national immunization days have demonstrated that VVMs can be used to remove heat labile polio vaccine from the cold chain for significant periods without compromising the potency of the vaccine. The use of VVMs can therefore facilitate outreach beyond the cold chain and help to overcome the cold chain space constraints associated with the increasing move toward single-dose vaccine presentations.

VVMs are also a powerful management tool to enable immunization programs to make changes to their cold chain infrastructures to minimize costs and decrease the chances of damaging freeze-sensitive vaccines. Once VVMs are on all vaccines, the level of vaccine wastage indicated by the VVMs could become the basis on which a particular cold chain is managed. Investment will be needed where wastage is high, and flexibility may be permitted where wastage is low. In this way, the cold chain may be "tuned" to eliminate costly redundancies inherent in the system today.

Status of Technology in 1996

PATH/HealthTech had worked with LifeLines Technology, Inc., (New Jersey) to successfully modify their proprietary heat-exposure monitoring technology for use with vaccines. These HEATmarker™ VVMs became commercially available in 1991 and were tested in more than 20 countries by WHO and PATH. The availability of VVMs facilitated the implementation of the "multi-dose vial policy" by WHO in 1995, which allows opened, multi-dose containers of liquid vaccine to be used for more than one day.

HEATmarker™ is a trademark of LifeLines Technology, Inc.

Activities 1996-2001

1996
- VVMs became available on all OPV procured by UNICEF, with no effect on the price.

1997
- OPV producers in India and Indonesia added VVMs to their vials.

1998
- WHO recommended inclusion of VVMs on all EPI vaccines.
- VVM impact study completed in Bhutan.
- VVMs facilitated OPV outreach during national immunization day in South Sudan and Somalia.
- PATH conducted VVM training for logistics officers in Africa.

1999
- WHO and UNICEF released a joint policy statement supporting the use of VVMs in immunization services, and UNICEF set an implementation date for full availability of VVMs on all EPI vaccines by 2001.
- PATH worked with CCL Label and Serum Institute of India to demonstrate VVM labeling on the caps of freeze-dried vaccine vials and ampoules.

2000
- PATH developed and published training materials in English, French, and Portuguese and printed for WHO/AFRO distribution with UNICEF funding
- PATH prepared a VVM Fact Sheet included in the UNICEF /GAVI *Vaccine and Immunization Products Guideline*–used in 50 GAVI country consultations.
- VVMs were included in the 2000 UNICEF vaccine tender for all vaccines, but only OPV suppliers complied.
- PATH assisted P.T. Bio Farma with identification, installation, and validation of equipment to label VVMs onto the packaging of Uniject™ prefill injection devices.

2001
- UNICEF included VVMs in their 2001-2003 vaccine tenders as well as the 2001-2003 Global Fund for Children's Vaccine/UNICEF tender. Shortly thereafter, UNICEF temporarily relieved vaccine manufacturers of this specification for all vaccines except OPV.
- PATH provided technical assistance to WHO, GAVI, and UNICEF to support their negotiations with vaccine producers.

Status of Technology in 2001

VVMs are currently available on vaccines produced by a total of 11 vaccine manufacturers in 9 countries (Belgium, Egypt, France, India, Indonesia, Italy, Japan, Korea, and Senegal). A number of non-OPV manufacturers are moving forward despite UNICEF's retraction. VVMs have already arrived on BCG vaccine in 11 countries; yellow fever vaccine in 9 countries; measles vaccine in 2 countries; and measles, mumps, rubella (MMR) in 4 countries (including 2 Pan American Health Organization [PAHO] countries—Colombia and Cuba). Negotiations between UNICEF, WHO, and the remaining vaccine manufacturers are ongoing.

Plans for the Future

During 2002, HealthTech will continue to work with the global task force (including WHO, UNICEF, USAID, and CDC) focused on ensuring VVM availability and assisting countries with introduction. A meeting with UNICEF vaccine suppliers is scheduled in Geneva in February during which a timeline for VVM implementation will be finalized. HealthTech will assist WHO with publication of VVM introduction packages for specific audiences (vaccine suppliers, vaccine purchasers, immunization programs, and health workers) during 2002 and will ensure that key information is documented and successfully transferred to other agencies.

Safe Injection Manual

Health Need Addressed

The spread of disease through unsafe injections is a long-standing concern among international health agencies. In immunization programs, improper reuse of injection equipment is the major cause of infections. Fortunately, several new types of syringes have been designed to prevent reuse. These AD syringes automatically become disabled after one use.

In 1999, WHO, UNICEF, and UNFPA published a joint statement recommending AD syringes as the equipment of choice for administering vaccines. Many countries are beginning to purchase AD syringes or receive them from donor agencies. While AD syringes are designed to require little or no instruction, initial practice sessions and guidance on the differences between various types can facilitate smooth introduction and minimize wastage of syringes. Additional information on how to administer injectable vaccines without harming the recipient, the health worker, or the community can also be provided through training sessions on AD syringes.

HealthTech III Solution and Potential Impact

With funding from BD and USAID, PATH developed a 98-page manual, entitled *Giving Safe Injections: Using Auto-Disable Syringes for Immunization*, intended for health workers who give injections in immunization programs located in resource-poor settings. As a training aid, it discusses current policies and practices for the delivery of safe injections, and includes specific instructions for each of the currently available WHO-approved AD syringes. This is particularly important, since each new design requires some variation in technique.

The following five lessons, or "chapters," can be presented by a trainer or used for self-study:

Chapter 1: The Health Impact of Unsafe Injections

Chapter 2: Selecting Safe and Effective Vaccines

Chapter 3: Reconstituting Vaccines Safely

Chapter 4: Safe Handling and Disposal of Sharps

Chapter 5: Using Auto-Disable Syringes

Status of Project in 2001

The manual can be downloaded from the PATH web site at the following online address: http://www.path.org/resources/safe-inj-pdf.htm. In addition to the English version of the manual, French and Russian translations were recently posted on the PATH web site. The manual may be reproduced or adapted to meet local needs with permission from PATH, provided the parts reproduced are distributed free or at cost, and not for profit. PATH may be able to supply original Adobe PageMaker or Adobe Acrobat computer files on CD-ROM, as well as instructions for adapting the manual.

Vaccine Reconstitution Technologies

Health Need Addressed

Some existing vaccines come in a freeze-dried form that must be mixed with sterile diluent just before injection. The mixing process requires an additional syringe and must be done properly to avoid contamination and ensure vaccine efficacy.

Meanwhile, new dried vaccine formulations are being developed that will allow safe storage of vaccines without refrigeration. These vaccines would have tremendous potential in extending the reach of vaccination programs and simplifying current equipment and logistics requirements. These highly stable vaccines of the future are expected to be available only in a dried form, requiring reconstitution at the point of use. Unfortunately, difficulties of the reconstitution process may be considered severe enough to discourage further development of stable, dried vaccines.

In addition to the extra equipment requirements of a mixing syringe and separate diluent vial, vaccines can become contaminated through several actions: contaminated needles used for reconstitution or dose delivery, wrong diluent used, incorrect amount of diluent used, and inappropriate storage of vaccine. Several deaths in developing-country immunization programs have been attributed to these issues.

HealthTech III Solution and Potential Impact

HealthTech is pursuing this problem in two parts: developing tools to improve the reconstitution process for currently available vaccines and investigating ways to further simplify the process for dried vaccines of the future.

- To overcome the problems associated with reconstitution of currently available lyophilized vaccines, HealthTech is working to simplify the tools and procedures required for the mixing process. Simplified and safer approaches are being developed.
- For future dried vaccines, the objective is to link the diluent and the dried vaccine in such a way that the reconstitution problems are eliminated. A simple, one-step process combining mixing and injection of a single dose—no more complicated than giving an injection with a liquid vaccine—is the ultimate goal.

Status of Technology in 1996

In 1996, the need for this technology had been identified, but HealthTech had not yet embarked on finding a solution.

Activities 1996-2001

- Assessed the feasibility of automatic reconstitution for single doses of measles vaccine using the propriety technology of PrisMedical Corporation. Testing demonstrated the feasibility of delivering vaccine with this technology within dose-consistency requirements (1999).
- Conducted a cost analysis of various syringe and vial configuration options for reconstitution of measles vaccine (1999).
- Conducted a market survey of commercially available lyophilized vaccines (1999).
- Collected patent and product information on available reconstitution technologies (1999).

Status of Technology in 2001

Reconstitution technologies are currently in the research- and idea-generation phases. An AD syringe with an integral plastic spike is under development. This approach could improve the safety of reconstitution of current vaccines by preventing reuse and human use of the mixing syringe.

Packaging of diluent in sterile dispensing containers configured with plastic septum-penetrating needles is feasible and could prevent many of these problems. Ideas for this packaging approach are being discussed with manufacturers.

A device such as the Uniject device could be used to power diluent through a dried-vaccine chamber and into the skin in one action. Simple demonstration models have been created to illustrate this concept.

Plans for the Future

Current reconstitution technology activities are focused on two areas:

- Identifying and developing ways to make reconstitution of current multi-dose lyophilized vials of vaccine (particularly measles) safer and easier.
- Developing easy-to-use systems to automatically reconstitute and deliver single doses of vaccines that have been dried using the new sugar-stabilization methods.

Needle-Free Injection System

Health Need Addressed

With the advent of the AIDS epidemic, and a clearer understanding of the transmission of hepatitis B and other bloodborne diseases through the use of unsafe needles worldwide, safe-injection technologies have become a high priority for international health agencies. Estimates indicate that more than 50 percent of developing-country injections are unsafe. Reuse of contaminated syringes, needlestick injuries among health workers, and threats to the community from improperly disposed of and contaminated sharps and needles are serious health risks. Multi-dose jet injectors, although credited with decades of use in the field, are no longer used due to evidence of cross contamination between injections. The availability of a safe and contamination-free, multi-dose jet injector would have great beneficial impact on public health worldwide.

HealthTech III Solution and Potential Impact

Under the HealthTech program, PATH has partnered with Felton Medical, Inc., of Kansas, and MedEquipment (earlier called Chemiautomatics Design Bureau—CADB), of Voronezh, Russia, in evaluating, testing, and refining the design of a multi-dose jet injector developed and manufactured by MedEquipment. This is a high-workload injector, intended for use in mass immunization campaigns. The design of the injector involves a novel and effective approach (a disposable protector cap between the nozzle and the site of injection) to eliminate cross contamination between injections, while maintaining a high rate of vaccine delivery to multiple patients.

This technology could provide significant improvements in safety, efficiency, and effectiveness of immunization programs. In particular, this device would be invaluable in providing the necessary immunization coverage required to control measles worldwide. Both immunization campaigns and health clinics would benefit from the use of this device through increased safety and reduced costs.

Status of Technology in 1996

During HealthTech I and II, PATH developed a considerable amount of knowledge and expertise in the area of jet injection for immunization including the following:

- Assessment of design and function of over 25 jet injector products and prototypes from various developers (1987-1999).
- Development of the MEDiVAX™ jet injector through human trials, World Health Organization (WHO) animal testing, and United States Food and Drug Administration (USFDA) market clearance.
- Development and refinement of bench-test protocols for jet injectors; distribution to WHO and interested manufacturers.
- Initial concept generation and design of the N-ject disposable-nozzle jet injector.

Unfortunately due to very stringent WHO standards for zero tolerance of cross contamination between injections, the MEDiVAX product was not introduced into the developing world.

™ MEDiVAX is a trademark of Program for Appropriate Technology in Health.

Activities 1996-2001

- Further design and iteration of N-Ject disposable nozzle jet injector (design halted in 1999 due to insurmountable challenges of cost to develop device).
- Start of collaboration with Felton Medical, Inc., for advancement of CADB jet injector system (BI-3M) for high-workload (mass campaign) applications (1998).
- Assisted with organization of the WHO/CDC conferences on needle-free jet injectors and presentation of appropriate designs for public health programs (1998-1999).
- Worked with CADB on contamination and performance bench testing, redesign of the BI-3M including autodisable protector cap (1999-2001).
- Conducted performance and verification tests on BI-3M, which were included in the 510(k) application submitted to USFDA (2001).
- Created ergonomically improved designs for inclusion in BI-3M redesign (2001).
- Conducted focus group discussion of new prototypes/ergonomic redesign for BI-3M (redesigned version designated BI-100) at recent joint SIGN/TechNet meeting in New Delhi, India (2001).

Status of Technology in 2001

The USFDA has recently granted 510(k) market clearance (#K013256) for the BI-3M, additional design changes will be incorporated, and a subsequent Special 510(k) will be submitted to the USFDA for the next generation BI-100 injector. An AD protector cap has been developed, which will be disabled after ejection from the nozzle face of the BI-100. Performance bench testing and user evaluation of this new protector cap design is currently in process.

Plans for the Future

PATH plans to continue collaboration with Felton in 2002, to focus on the following areas:

- Protector cap packaging design and handling
- Performance bench testing of BI-100 and AD protector cap
- User evaluation of BI-100 with AD protector cap in developing country field setting
- Identification of optimal and appropriate operational steps for use in the developing world
- User instructions and training materials for BI-100
- Coordination with policy makers in international public health to promote acceptance and introduction of BI-100

Safe Medical Waste

Health Need Addressed

Each year, more than 12 billion injections are administered worldwide. Estimates indicate that more than 50 percent of developing-country injections are unsafe.[2] Safe injection is a high priority for WHO, but the global target set by WHO and UNICEF to provide greater than 95 percent safe injections by the year 2000 is far behind schedule. Safe needle and syringe disposal is an important element of these injection safety goals.

WHO is encouraging use of AD syringes as a tool against syringe reuse. Ironically, the increased use of AD syringes will result in an increase of contaminated needles and syringes that require disposal. Healthcare workers who handle an increasing volume of contaminated syringes and needles are at risk of needlestick injury, which can result in transmission of numerous bloodborne diseases such as hepatitis B, hepatitis C, and HIV. Improper disposal of these needles presents a serious risk to the medical waste disposal workers and to the community at large.

HealthTech III Solution and Potential Impact

An immediate need exists for a needle disposal system that is simple, inexpensive, and requires minimal handling of the contaminated needle by the user(s). Point-of-use needle removal ("defanging") and needle storage provides immediate isolation of the contaminated sharps, decreases required disposal-box volumes, and may aid in discouraging reuse. Bundling or integrating a needle-removal/containment device with the needles and syringes will facilitate the safe handling and disposal of needles, increase awareness, and provide an example of an integrated and complete "use-and-defang" disposal system.

Any situation in which a needle and syringe are used is an appropriate setting for point-of-use needle removal and segregated safe containment. This technology would improve safety for large-scale immunization campaigns as well as for smaller outreach clinics.

Status of Technology in 1996

HealthTech had anticipated the need for technologies to deal with waste disposal in 1996, but efforts at that time were mainly focused on the development of AD syringes. The primary efforts in this area have occurred during HealthTech III.

Activities 1996-2001

- Evaluated seven electrical and chemical needle destroyers to support WHO specifications for evaluation of needle destroyers (1997-1998).
- Investigated feasibility of syringe melters as safe disposal technologies (1999).
- Conducted in-house user and technical evaluation of ten currently available needle destroyers from nine manufacturers (1999).

[2] *WHO Injection Safety, Quality of Immunization Services [QIS]*, August 28, 1998.

- Collected marketing and technical information from ten needle-destroyer manufacturers (1999).
- Drafted a “decision tree” approach to medical waste disposal options (1999).
- Developed numerous concepts for safe medical waste disposal at the point of use, including luer slip needle removers and universal needle pullers (1999-2000).
- Advanced luer-slip needle removal concept to prototype form and developed complete technical briefs which were then distributed to five manufacturers and WHO (2000-2001).
- Advanced universal needle puller concept through several prototype design generations, and evaluated one design in four immunization settings in India (2001).
- Commissioned market and opportunities study for needle pullers in India (2001).

Status of Technology in 2001

The primary technologies that have been developed during HealthTech III have been an inexpensive universal needle puller and a luer-slip needle “popper” can. The latter is a fairly low-tech solution and has been made available for public sector use. Meanwhile the puller is currently being redesigned based on the field assessment in India and based on a need identified by the Bill and Melinda Gates Children’s Vaccine Program in Andhra Pradesh, India. A patent application has been filed, and a search for Indian manufacturers is being conducted.

Plans for the Future

HealthTech is pursuing a mix of technology solutions for the appropriate "defanging" and disposal of needles. HealthTech will redesign and evaluate the needle puller and look at its utility as a stand-alone device or integrated with a medical waste disposal system. HealthTech will continue to analyze the field situations where injections are administered, and will develop and refine technologies for sharps disposal that are easy to use, appropriate, and inexpensive.

Basic Delivery Kit

Health Need Addressed

High rates of maternal and perinatal mortality in developing countries indicate a crucial need for new and innovative interventions for pregnancy and neonatal care. Most women have no access to maternity services due to distance, cost, and local customs; many give birth alone. High rates of neonatal and maternal tetanus and sepsis indicate a need for education and materials focused on clean birth practices.

HealthTech III Solution and Potential Impact

The basic delivery kit is an inexpensive, simple cord-care kit designed for use in home births. Based on a needs assessment in rural community settings in Nepal, the purpose of the kit is to provide items that will encourage clean delivery practices. The contents of the kit developed in Nepal include pictorial instructions, a small bar of soap, a polyethylene delivery sheet, a cord-cutting surface, cord ties, and a clean razor blade. The delivery kit is designed for use by trained and untrained traditional birth attendants, family members, and women who give birth unassisted in the home.

Status of Technology in 1996

Prior to 1996, the delivery kit used in Nepal had been developed by Save the Children/US and its partners, with technical assistance from HealthTech and USAID/Nepal. UNICEF and UNFPA also provided funds. The Nepali MOH has officially approved the kit. A private, Nepali, women-owned company, Maternal and Child Health Products Pvt., Ltd. (MCHP), was set up to produce and distribute the kits to wholesalers and retailers through social marketing distributors and nongovernmental organizations, and to traditional birth attendants through training programs supported by the MOH. MCHP is a self-sustaining organization and has produced and sold approximately 500,000 delivery kits.

Activities 1996-2001

- HealthTech undertook a quantitative evaluation of the delivery kit in Nepal, which demonstrated a positive correlation between kit use and a reduction in simple cord infection (1997-1998).
- PATH sponsored a delivery kit conference in Nairobi, Kenya (March 1999).
- PATH made presentations on delivery kits at multiple international health conferences focused on maternal and neonatal health.
- Published the *Basic Delivery Kit Guide*, a comprehensive how-to manual on delivery kit design, development, distribution, promotion, evaluation, and research.

Status of Technology in 2001

Despite the difficulty in evaluating the impact of delivery kits throughout the world, there is evidence that use of simple delivery kits can have a positive impact upon birthing practices and related disease outcomes. In addition to the tangible benefits of kit use—having clean hands, a clean surface, and a clean cord—these activities can enhance positive birth outcomes through improved awareness of clean birth practices.

Plans for the Future

Following a PATH-sponsored delivery kit conference that took place in Nairobi, Kenya, in March 1999, several African countries requested PATH's technical assistance in their safe motherhood or maternal and child health programs to implement the development, promotion, and use of delivery kits. PATH, in collaboration with the MOH and the National Institute of Medical Research (NIMR), is conducting another combined quantitative/qualitative evaluation of the single-use UNFPA delivery kit in Mwanza, Tanzania. The results will help to verify the earlier study in Nepal. This will help decision-makers of programs in considering introduction of delivery kits as an appropriate, effective health intervention.

ICS Test for Tuberculosis

Health Need Addressed

Tuberculosis (TB), a bacterial disease caused by *Mycobacterium tuberculosis*, is a major health problem in the developing world as well as a disease that is re-emerging as a major health threat in the developed world. High prevalence in some developing-world countries is associated with HIV infection and AIDS. WHO statistics indicate there are 20 million cases of active TB worldwide, and approximately 8 million new cases occur each year. TB has the highest mortality rate of any infectious disease in the world, and results in approximately 3 million deaths annually. TB is a highly contagious disease, which can be difficult to identify and diagnose accurately. Since it is curable with a course of antibiotic therapy, early diagnosis and treatment can curtail the spread of the disease within the general population.

HealthTech III Solution and Potential Impact

The ICS test for tuberculosis, developed during HealthTech III, utilizes relatively inexpensive, off-the-shelf components, and is formatted to identify specific serum antibodies to recombinant proteins specific to *Mycobacterium tuberculosis*. A test can be completed in 15 to 20 minutes and can be performed by technicians with minimal training. This test will allow tuberculosis testing to be performed directly on blood, serum, or plasma samples from patients in rural or smaller clinics or hospitals in the developing world or in resource-limited settings. Accurate results can be returned within the same hour or day, allowing more effective patient follow-up and counseling. The test also has potential use in the United States, Canada, and Eastern Europe where TB is on the rise in HIV-positive individuals and in medically underserved populations.

Status of Technology in 1996

Since 1996, WHO has promoted the Directly Observed Therapy Short Course (DOTS) strategy for TB control, one aspect of which is case detection through sputum smear microscopy of TB suspects. The emphasis on TB diagnosis by sputum smear microscopy is, however, problematic. The method is simple and relatively inexpensive but requires quality microscopes, experienced microscopists, and exacting quality control. Although enzyme-linked immunosorbent assay (ELISA) based serological tests and several rapid serological tests have been commercially available for several years, most—if not all—of these tests lack the necessary sensitivity and specificity to have any clinical utility. This is particularly the case in HIV positive populations.

Activities 1996-2001

- Collected and/or acquired well-characterized sera from TB patients to be used in developing a rapid test (1998-1999).
- Optimized selected antigens for use in initial prototype of the test in the ICS format; compared performance of ICS test to commercially available TB tests (1999-ongoing).
- Finalized a collaboration agreement between PATH and antigen manufacturer for eventual commercialization of the TB ICS test (2001).
- Conducted cost analysis and use assessment of the TB ICS test in Ukraine (1999).

- Developed detailed clinical study protocols to conduct prospective clinical evaluations of the PATH TB ICS test in India, Ukraine, Zimbabwe, and Botswana (2001).
- Actively participated in the WHO TB Diagnostics Initiative (2000-present).

Status of Technology in 2001

Research and development of a TB test in the ICS format are almost completed and the test is performing satisfactorily with serum samples collected from different geographic regions and from HIV-seropositive individuals. In preliminary retrospective testing of sera from India, Indonesia, Brazil, and several African countries, the overall sensitivity and specificity in HIV negative populations is greater than 70 percent and 90 percent respectively.

Plans for the Future

Under HealthTech IV, PATH will assess the clinical performance of the TB ICS test in several well-controlled evaluation sites. Their outcome will determine if the current test meets the WHO/CDC minimal performance criteria or if additional research and development is required to improve test performance. PATH will then develop a commercialization strategy for the TB ICS test with the antigen manufacturer. PATH will also continue to participate in the WHO TB Diagnostics Initiative (TBDI) program to evaluate the performance of other new serological tests for TB.

ICS Test for Falciparum Malaria

Health Need Addressed

More than two billion people live in malarious regions of the world. As a result, more than 300 million new cases of malaria occur each year, resulting in several million deaths worldwide. Microscopy is the standard method for diagnosis in many parts of the developing world, but it requires considerable technical skill to perform well and is time consuming. Therefore, an alternative test method is urgently needed for the rapid and accurate identification of falciparum malaria infection in smaller clinics and hospitals in which microscopy cannot be adequately performed.

HealthTech III Solution and Potential Impact

The falciparum malaria ICS test, developed during HealthTech III, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify *plasmodium falciparum*-specific, histidine-rich protein 2 (PfHRP-2) antigen in blood. A test can be completed in 20 minutes and can be performed by technicians with minimal training. The simple, rapid technology will allow testing for falciparum malaria in rural or small clinics or hospitals in the developing world so that accurate results can be returned the same day. The test can also be used by epidemiological surveillance teams in the field to gather baseline data or to assess the effect of public health interventions. The tests can supplement or confirm infection in conjunction with microscopic diagnosis of malaria at central reference facilities.

Status of Technology in 1996

Prior to 1996, PATH had developed rapid tests for infectious diseases primarily in a dipstick format. At the start of HealthTech III, PATH switched to developing a new core platform for rapid tests – the ICS format. After six months, the format was ready to be applied to specific applications like malaria.

Activities 1996-2001

- Signed collaboration agreement with Omega Diagnostics for codevelopment of ICS test.
- Developed and validated rapid, low-cost ICS version of malaria test and conducted field evaluations in Peru and Malawi.
- Transferred technology to producers in Canada, India, and Germany. Assisted several commercial producers to facilitate their malaria test development.
- Participated in a WHO/USAID-sponsored workshop to determine appropriate specifications for malaria diagnostic test; developing introduction strategies for all rapid malaria tests.
- Developed a decision tool for program managers to choose the appropriate malaria test for their particular situation.
- Worked with international health agencies in advancing and introducing the entire range of rapid malaria tests available from commercial competitors into use in developing countries.

Status of technology in 2001

The malaria ICS test has been evaluated in the laboratory as well as under field conditions in the developing world, in Peru and Malawi. The evaluations demonstrated a sensitivity of over 96 percent, and specificity of 93 percent or more. Ease-of-use studies have also concluded that the test is extremely easy to interpret. Technology transfer to three manufacturers is now complete. During the past six years, many commercial companies have now produced rapid malaria tests at affordable prices, so many of the needs of developing countries are being met.

Plans for the Future

PATH is closing out activities funded by HealthTech; however, future plans include completing the development and transfer of production capacity of *P. falciparum* monoclonal antibodies, maintaining the rapid diagnostic web site, and finalizing a web-based version of the cost-effectiveness decision tool for managers.

ICS Test for Syphilis

Health Need Addressed

Syphilis is an STD caused by *Treponema pallidum*; it can easily be treated with antibiotic therapy. If the infection remains untreated, however, syphilis may eventually cause long-term, debilitating effects that are potentially fatal. Pregnant women who are infected can pass the disease to their newborn infants, where it can produce systemic infection and death. Syphilis infection also increases the risk of contracting HIV and other STDs. Syphilis remains underdiagnosed and undertreated in most of the developing world where access to testing is limited. Currently available screening tests are time-consuming and/or complex, confirmatory testing is slow or unavailable, culture diagnosis is not possible, and syndromic management fails to detect asymptomatic infections. Therefore, an alternative test method is urgently needed for the rapid and accurate identification of syphilis to be used in antenatal clinics and other screenings.

HealthTech III Solution and Potential Impact

The ICS test, developed during HealthTech III, uses relatively inexpensive components and is formatted to identify specific serum antibodies to a recombinant surface protein specific for *T. pallidum*. A test can be completed in 15 to 20 minutes by persons with minimal training. The strips are stable for one to two years at ambient temperatures when packaged appropriately, and built-in controls indicate whether each strip performs correctly. This simple, rapid test is designed to test serum or plasma samples from patients in settings where conventional screening tests cannot be performed, in order to facilitate delivery of appropriate treatment. This test has potential for use as a screening, diagnostic, or confirmatory test. Also, during the course of the last six years, other rapid syphilis tests have been developed by commercial companies; PATH has played a role in encouraging the introduction of the full array of tests.

Status of Technology in 1996

No affordable, rapid field tests for syphilis were available for developing world use in 1996.

Activities 1996-2001

- Together with Omega Diagnostics (Alloa, U.K.), PATH codeveloped, optimized, and validated an ICS test format for diagnosis of syphilis
- Worked with CDC to validate the ICS test on 738 frozen, stored serum specimens from South Africa.
- Transferred technology for production of the rapid syphilis ICS test to Quorum Diagnostics (Vancouver, B.C., Canada), a subsidiary of Omega Diagnostics, in 1998.
- Provided technical assistance to Orchid Biomedical Systems (Goa, India) in the development and evaluation of an ICS test for syphilis (1999).
- Developed a generic global introduction strategy for rapid syphilis tests inclusive of all qualifying commercial tests from any source (1999).

Status of technology in 2001

Development of an ICS test to detect antibodies to a specific *T. pallidum* protein has been completed. Results of validation studies conducted in high and low-risk populations show that the test is accurate, easy-to-use, and provides an effective alternative to RPR in settings where RPR is difficult to perform. Results were presented at the International Society for Sexually Transmitted Diseases Research meeting (Berlin 2001).

Plans for the Future

The ICS whole blood test for syphilis is a new technology that addresses a clear public health need. PATH's experience with technology introduction has led to a strategy of identifying constraints to widespread use of a technology and then working to overcome these constraints. Activities are planned to demonstrate the feasibility and cost-effectiveness of the test, build institutional support for, disseminate information on, and investigate other appropriate uses for these tests. Development of a test that can be used with whole blood is underway, and commercialization of this PATH technology is in progress.

ICS Test for Gonorrhea

Health Need Addressed

Despite long-standing, global, public-health efforts to control STDs, *Neisseria gonorrhoeae* (gonorrhea) infections still occur in epidemic proportions in the developing world and in specific regions of the United States. For effective control of gonorrhea, STD-control programs must offer early and accurate diagnosis of symptomatic infection and identification of invasive, complicated, or asymptomatic infections. Control of STDs is also considered to be an essential component in control of HIV/AIDS transmission.

HealthTech III Solution and Potential Impact

The ICS test for gonorrhea, being developed under HealthTech III, utilizes relatively inexpensive, off-the-shelf components, and is formatted to identify a specific gonoccocal antigen obtained directly from clinical specimens. The strips are stable at ambient temperatures, if packaged appropriately. This simple, rapid test will allow testing to be performed on direct clinical specimens from patients in rural or smaller clinics or hospitals in the developing world or other resource-limited settings. Accurate results can be returned within the same hour or day, thereby allowing effective patient follow-up, additional counseling, and prescription of therapeutic drugs, if needed. The tests may also be used by epidemiological surveillance teams in the field to gather baseline data, or to assess the effect of public-health interventions.

Status of Technology in 1996

In much of the developing world, diagnosis of gonococcal infection was inadequate in 1996 and still is today, because available tests are relatively expensive and/or complex, culture diagnosis is unavailable, and syndromic diagnostic protocols for women are largely inadequate.

Activities 1996-2001

- Determined that a rapid gonorrhea (GC) ICS test using monoclonal antibodies (Mabs) and the major outer membrane protein (MOMP) as the target antigen lacked a basic, intrinsic level of sensitivity and specificity necessary to attain clinical diagnostic utility (1996-1999).
- Established collaboration with ThermoBioStar (Boulder, CO) on the development of a simple and rapid GC ICS test using a non-MOMP antigen target for GC (2000).
- Established proof-of-concept for use of the BioStar reagents in a GC ICS test using the Mab as signal and polyclonal serum as capture (2000).
- Discussed a PATH/ThermoBioStar collaboration for the GC ICS test with ThermoBioStar's partner, Asahi Chemicals (Tokyo, Japan), to determine marketing territories (2000).
- Optimized the GC ICS test and determined the analytical sensitivity and specificity of the assay (2001)
- Obtained well-characterized clinical specimens for use in determining the clinical performance of the GC ICS test (2001).
- Identified several potential sites for prospective field evaluation of the GC ICS test (2001).

Status of Technology in 2001

Although a limited number of manufacturers have marketed rapid tests in the last five years, the state of rapid tests for gonorrhea has not changed much since 1996, due to technical complexities in designing a diagnostic for this infectious disease. In-house evaluation of the marketed tests have

indicated that the tests lack the necessary specificity for them to have any clinical utility. Although the HealthTech test kit is not yet commercially available, field evaluation will soon be underway.

Plans for the Future

Over the last year, the GC diagnostic team has optimized the ICS test format and is in the process of evaluating it with clinical specimens from the University of Alabama, University of Washington, and the British Columbia Center for Disease Control.

Initial discussions have been held with collaborators in India, the Philippines, and South Africa for prospective clinical field evaluation of the GC ICS test. Next steps will include identifying a commercial partner for technology transfer of the manufacturing capability and finalizing the terms of the reagent supply agreement with ThermoBioStar.

ICS Test for Chlamydia

Health Need Addressed

Despite long-standing, global, public-health efforts to control STDs, *Chlamydia trachomatis* infections still occur in epidemic proportions in the developing world and in parts of the United States. WHO estimates there are 333 million new STD infections every year. For more effective control, STD-control programs must offer early and accurate diagnosis of symptomatic infection and identification of invasive, complicated, or asymptomatic infections. Control of STDs is also considered to be an essential component in control of HIV/AIDS transmission.

HealthTech III Solution and Potential Impact

The ICS test for chlamydia, that PATH has been developing under HealthTech III, utilizes relatively inexpensive, off-the-shelf components, and can identify specific chlamydial antigens using cervical or urethral swabs. The test can be completed in 15 to 20 minutes by technicians with a minimum of training, this allows testing to be performed on direct clinical samples from patients in rural or smaller clinics. Accurate results can be returned within minutes, thereby allowing effective patient follow-up, additional counseling, and prescription of therapeutic drugs, if needed. Epidemiological surveillance teams may also use this test to gather baseline data or to assess the effect of public-health interventions.

Status of Technology in 1996

The Unipath MF test was originally the only rapid diagnostic test available for *C. trachomatis.* The test required a complicated heat extraction step and was cost prohibitive for use in resource-limited settings. In 1995, PATH initiated research and development under HealthTech funding on a rapid ICS test format for detection of *C. trachomatis,* which was then continued under HealthTech III.

Activities 1996-2001

- Determined that the extraction procedure should be reformulated and that alternative monoclonal antibodies needed to be accessed. In addition, since new molecular test formats combined testing for *C. trachomatis* and *Neisseria gonorrhoeae*, it was determined that the assay platform should include the capability to use a single specimen for both tests (1997).
- Intensified product development activities through a collaboration with Alchemy Laboratories (Dundee, UK); investigated alternative reagents and test formats (1998).
- Established, evaluated, and optimized an improved immunoassay format for the detection of *C. trachomatis* with archived clinical specimens. Established essential equivalence in sensitivity and specificity between the Unipath MF (the established reference standard) rapid chlamydia test and the PATH test (1999).
- Investigated the feasibility of developing an alternative test system—a relatively simple molecular diagnostic test for *C. trachomatis* and *N. gonorrhoeae,* but determined this was not appropriate for use in peripheral, developing-country settings (2001).

Status of Technology in 2001

The Unipath MF is still the only established rapid diagnostic test available for *C. trachomatis,* since the PATH test kit is not yet commercially available. Initial laboratory evaluations of the PATH ICS test for chlamydia indicate that it is possible to eliminate the heat extraction system used in the Unipath MF test. In addition, laboratory data indicates that the PATH ICS test reacts with all chlamydia serovars and is as sensitive as other commercial tests using a limited panel of clinical

specimens. However, ambiguities in the clinical performance of the test with samples from the University of California and the University of Alabama were recently identified, and additional research and development efforts are necessary to resolve these observed differences in performance.

Plans for the Future

PATH has proposed that HealthTech IV funding be used to complete the groundwork to provide solid, unequivocal clinical performance data on which to base a decision to proceed with prospective test evaluations or to end team activities. If the team determines that the test truly has adequate performance characteristics, it would then approach potential donors to request additional funding to implement a field trial.

Molecular Platform Diagnostics

Health Need Addressed

Despite long-standing, global, public-health efforts to control STD, *Neisseria gonorrhoeae* (gonorrhea) and *Chlamydia trachomatis* (chlamydia) infections still occur in epidemic proportions in the developing world and in specific regions of the United States. For effective control of gonorrhea, STD-control programs must offer early and accurate diagnosis of symptomatic infection and identification of invasive, complicated, or asymptomatic infections. Control of STDs is also considered to be an essential component in control of HIV/AIDS transmission. Conventional methods for detection of *N. gonorrhoeae* and *C. trachomatis,* such as culture, syndromic diagnostic protocols, and EIA, do not detect infection in many patients due to an intrinsically lower assay sensitivity.

HealthTech III Solution and Potential Impact

During HealthTech III, PATH and USAID decided to understand the feasibility of developing less expensive, simpler, and faster nucleic acid amplification (NAA) tests for *N. gonorrhoeae* and *C. trachomatis.* These attributes would make it easier for STD-control programs to diagnose symptomatic as well as asymptomatic infections as part of their effort to identify gonococcal and chlamydial infections, and would help to control HIV/AIDS transmission.

An NAA test method for gonorrhea and chlamydia will allow testing to be performed on direct clinical specimens. Accurate results could be returned within the same day, thereby allowing for effective patient follow-up, additional counseling, and prescription of therapeutic drugs, if needed. The tests might also be used by epidemiological surveillance teams to gather accurate baseline data or to assess the effect of public-health interventions. The tests could also be used by central reference facilities to confirm gonococcal and/or chlamydial infections.

Status of Technology in 1996

In 1996, NAA tests were considered more sensitive than conventional methods for the detection of these infections. New molecular techniques were becoming commercially available for GC and CT and were revolutionizing diagnostic microbiology laboratories around the world. However, all commercially available NAA tests were then still too complex, relatively expensive, and require highly skilled personnel to run them.

Activities 1996-2001

- Completed assessment of the feasibility of simplifying and making these tests appropriate for developing world use (2000-2001).
- Collaborated with an expert in the molecular biology of gonorrhea and chlamydia from the University of Washington conducted on the development of a multiplex polymerase chain reaction (PCR)-based nucleic amplification step (2000).
- Began work on the development of a simple and rapid nucleic acid extraction system to enable urine to be used as the clinical sample. (2001)
- Assessment on the needs and opportunities for use of molecular diagnostics for detection of gonorrhea and chlamydia in the developing world completed (2001).

Status of Technology in 2001

Although molecular platform-based technologies are rapidly changing how testing is done in well-equipped laboratories, research has shown that these technologies are not yet ready for developing-country use. They are still technically complex and would be too expensive to produce. A market assessment of the need in developing countries for such tests did show a potential market, but only if the test is affordable and easy. PATH has currently recommended to USAID that further research and development of NAA tests for developing-country use would not be a suitable investment of public-sector funding at this time.

Vitamin A Test

Health Need Addressed

For almost 50 years, researchers have known that the consequences of severe vitamin A deficiency (VAD)—including blindness and death—could be prevented by administering oral doses of vitamin A. Analysis of over 150,000 children between the ages of six months and five years, from several vitamin A-deficient countries, indicate that almost one-quarter of early childhood deaths, especially deaths related to diarrhea and measles, could be prevented by ensuring that children receive sufficient vitamin A. Public health planners and researchers need easy, inexpensive ways to assess the extent of VAD among populations in order to inform policy makers and promote well-targeted vitamin A programs.

HealthTech III Solution and Potential Impact

The RBP-EIA was developed at the request of USAID as a rapid, inexpensive test to quantify RBP from individual serum specimens, using RBP as a surrogate marker for retinol. The test is rapid; results are available in as little as 35 to 40 minutes after starting the assay. The strip wells can be read on a standard or portable EIA reader. It is designed for use in laboratories at the provincial- or district-hospital level, or by trained epidemiological surveillance teams. Application of the test will allow health care workers to assess the extent of VAD within populations, determine nutritional status, and implement the appropriate intervention. The RBP-EIA has been designed to produce data rapidly; to reduce reliance on costly, centralized laboratory facilities; and to provide an effective tool for field monitoring and recognition of VAD in at-risk populations.

Status of Technology in 1996

In 1996, there were only relatively sophisticated, technically demanding, and costly tests available, which used the detection of serum retinol as a surrogate marker for VAD. In 1994, PATH had performed a preliminary study to determine feasibility of developing a simple, rapid, and inexpensive diagnostic for VAD. As a result of recent publications, RBP was explored as a surrogate marker for serum retinol.

Activities 1996-2001

- PATH developed an EIA for the quantification of RBP that resulted in a good correlation between the RBP-EIA and serum retinol values on samples in the laboratory (1996-1997).
- PATH evaluated the RBP-EIA in Guatemala at the Institute of Nutrition of Central America and Panama (INCAP). Serum samples correlated closely with high-performance liquid chromatography (HPLC) retinol values, but plasma samples did not (1998).
- Technical assistance and training were provided on the use of the RBP-EIA to the MOH in Madagascar, in preparation for the planned national nutrition assessment (2000).
- Laboratory validation results were presented at the International Vitamin A Consultative Group meeting in Hanoi, Vietnam (2001).
- RBP-EIA and HPLC retinol concentrations were determined for 393 serum specimens obtained in a national VAD survey in Cambodia. Results were positive (2001).

Status of Technology in 2001

This diagnostic tool has been shown to be robust and user friendly during laboratory verification exercises. The verification protocols include Analytical Performance Characteristics, Interfering Substances testing, and a field verification trial.

- Analytical Performance Characteristics of the RBP-EIA were established using guidelines from the U.S. Pharmacopeia & National Formulary (USP 24/NF19, section 1225, Validation of Compendial Methods, pages 2149-2152). These characteristics included accuracy, precision, detection limit, quantitation limit, intra-assay variability, linearity, range, and analyte recovery.
- Interfering Substances testing determines the effects of endogenous and exogenous substances on analytical test results obtained when testing RBP concentration in serum samples using the RBP-EIA. Ultimately, this information may be used in establishing limitations and claims in product labeling.
- Field Verification testing- RBP-EIA and HPLC retinol concentrations were determined for 393 serum specimens obtained in a national VAD survey in Cambodia.

In all cases the RBP-EIA's performance was excellent and provided great feedback regarding the design and suitability of the RBP-EIA as a rapid, quantitative tool for the assessment of VAD in populations, by establishing its limitations and strengths.

Plans for the Future

PATH has proposed the following pans for the future:

- Development of advocacy materials for all stakeholder groups on the use of VAD testing for policy and program development and on the appropriate use of the product in the field.
- Ensuring an adequate source of supply through the transfer of the RBP-EIA to a commercial manufacturer.
- Further refinement of the RBP-EIA for use with dried blood spots with both venous and capillary blood samples.
- Promotion of an early adopter's program to promote the introduction and appropriate use of the technology.
- Support the development of a battery-operated strip well reader to make the test easier to use in a field setting.

IV. Report of Field Support, Add-On, and/or Mission-Funded Projects

During the course of the six years, PATH has received one MAARD and field support funding from several Missions and other divisions at USAID for complementary work under the HealthTech cooperative agreement. Three field support projects, which were carried out under HealthTech, were substantial and related closely to other work undertaken by HealthTech. These include:

Field Support Projects

A. Schistosomiasis Vaccine Development Program, USAID/Egypt

Health Need Addressed

Schistosomiasis affects approximately 200 million people worldwide, and over 85 percent of these are in Africa. Two species infect people in Africa, *Schistosoma haematobium* and *S. mansoni*. The former is relatively easy to diagnose because of the classical symptom of blood in the urine. It is also easy to treat with a single oral dose of praziquantel, a generic drug costing less than 25 cents per treatment. *S.mansoni,* while equally easy to treat, is very difficult to diagnose (and expensive compared to the cost of treatment). There is no specific symptom when infected, and yet the long-term consequences are devastating. A vaccine capable of protecting children from infection would be a tremendous tool for the control of this disease. The proof of principle had been established by irradiating larval worms and protecting laboratory animals against *S. mansoni* and cows against *S. bovis*. In 1995 six candidate vaccines were identified by a WHO committee which investigated the status of vaccine development. Two of these candidates were selected for development including Phase One human trials supported financially by USAID Cairo, under the Schistosomiasis Vaccine Development Project (SVDP).

HealthTech III Solution and Potential Impact

SVDP was a complex project involving eight partners, of which three participating partners were situated in Egypt–The Egyptian Reference Diagnostic Center (ERDC); the High Institute for Public Health, Alexandria, (HIPH); and the US Navy Medical Research Unit, Cairo, (NAMRU-3). There were two US Government partners; CDC, Atlanta and NIAID, Bethesda. The remaining three other partners involved included PATH, Seattle; Harvard School of Public Health (HSPH), Boston; and Bachem, a commercial immunology company based in California. With funding provided from the USAID mission in Egypt, through HealthTech III, PATH was responsible for project and administrative management, procurement, arrangements for training and travel, human subjects protection procedures, intellectual property rights issues, and subcontracting the services required from both the HSPH and Bachem.

Status of Project in 1996

PATH was not originally involved in the project; another contractor was responsible for the technical and administrative management. However, USAID had difficulties with renewing their contract, and for various reasons invited PATH to participate in the project starting in 1998.

At that time the project scientific design of the original project was as follows:

- The two selected vaccine candidates would be purified in their respective laboratories–one at HSPH and one at NIAID.

- When purified material was prepared, it would be concurrently independently tested at CDC and ERDC.
- For one of the candidates (called MAP-4), Bachem was employed to produce a good manufacturing practices (GMP) quality sample and then proceed to GMP production of larger quantities for testing in human subjects.
- In Cairo, the ERDC would carry out human correlate studies on each vaccine candidate batch produced.
- At the National Institutes of Health and CDC, preparations would be made for the first human Phase I testing of a schistosomiasis vaccine candidate.
- At the HIPH, stool samples would be examined from a cohort of subjects to prepare for the correlate studies and eventually a vaccine test in the field.

Activities 1998-2001

PATH fulfilled its obligation to USAID Cairo under HealthTech III by:

- Providing the SVDP with a Resident Project Manager based in Egypt.
- Procuring and shipping all the equipment and supplies requested by the ERDC.
- Providing an internal review board for all human subject contacts.
- Protecting the intellectual property rights issues for all parties.
- Training Egyptian scientists as required in immunodiagnostic techniques,
- Arranging all travel to conferences, and travel to and from Egypt for consultants.
- Arranging all Technical Advisory Group (TAG) meetings for the project every six months.
- Assisting with publication of results in recognized scientific journals.
- Providing regular supplies of scientific journals and computer software updates.

Status of Project in 2001

The Project was originally designed for a five-year life to end in September 2001. The project will now be completed by September 2002 (during HealthTech IV). By the end of the project, neither of the vaccines will have reached the stage of completion of a Phase I test.

The candidate MAP-4 did not succeed in passing the testing stage for two reasons, and therefore the final planned stages of development could not be attained. The first problem was that the GMP production was deemed by Bachem to be beyond the current technical capabilities. GMP quality could be prepared only in very small quantities, and the process could not be reproduced to FDA standards. The second problem was that the major premise for selecting MAP-4 as a candidate was its ability to protect mice from infection. Testing of the nearly pure material showed that in the purification process, the material had lost its protective capacity. This then invalidated the argument for MAP-4 as a vaccine candidate.

The second candidate, paramyosin, was considered the less likely of the two candidates at the start of the project; however after some initial problems, the molecule was purified, and it is now being tested for protection in mice and scale-up production. Because of time and funding constraints, the SVDP will be closed before we learn whether paramyosin would be a candidate for human testing. However, the development work has been done and is available to other funding groups to take over where USAID funding will leave off.

Plans for the Future

PATH is expecting to receive funding for an additional 12 months in order to complete the project. The remaining tasks to be completed include final testing of paramyosin purified samples in animals and human correlate tests, continued field site preparation, fulfillment of human subjects research procedures, publication of scientific results, preparation for a final TAG meeting, and writing a final report.

B. Program for Advancement of Commercial Technology - Child and Reproductive Health, USAID/India

Health Need Addressed

Increased commercial-sector involvement is necessary for the introduction and correct use of high-quality child and reproductive health technologies. PATH is providing technical assistance to the Program for Advancement of Commercial Technology-Child and Reproductive Health (PACT-CRH), a five-year, $20 million program that promotes the health and nutrition of the Indian people. PACT-CRH is funded by the USAID Mission in India and is managed by the Industrial Credit and Investment Corporation of India. Underway since 1996, the program promotes ventures that develop products and services related to child survival, the provision of contraceptives, and the prevention of STDs, including HIV.

PATH's primary role in PACT-CRH has been to provide technical assistance related to the introduction of new technologies. As of August 1998, additional field support was provided to PATH through HealthTech by the USAID Mission in India in support of this project.

Activities 1996-2001

- Provided technical assistance to PACT-CRH loan recipients and reviewed technical proposals.
- Supported PATH India costs for a comprehensive communications campaign for the generic promotion of oral rehydration therapy, including training of doctor's and support for Oral Rehydration Salts (ORS) Day.
- Facilitated transfer of 10 different technologies from the HealthTech project which are now made or used in India, including three AD syringes, sharps disposal technologies, hepatitis B in Uniject devices, and VVMs.
- Transferred technologies and provided follow-on assistance for rapid pregnancy, syphilis, malaria, and diphtheria diagnostics.
- Reviewed and assessed sharps disposal technologies. HealthTech/PACT funding significantly accelerated the design review and commercialization timetable for the needle puller.
- Identified a U.S. source of vaccine preservation technology and facilitated negotiations between the source and a major Indian vaccine manufacturer.
- Provided technical assistance on GMP to several manufacturers.
- Provided technical assistance on condom manufacturing in several different areas, including specifications for packaging and production.
- Organized an expert panel at the AIDS 2000 conference in Madrid to promote the development of rapid diagnostics for HIV and STDs in India.

Status of the Project in 2001

HealthTech has played a key role in incubating the rapid diagnostics market in India by providing technical assistance to six firms and transferring five simple, rapid diagnostic tests to India for local

manufacture. In addition, HealthTech played a role in the incubation of the "safe injection" products industry in India by supporting introduction activities for three autodisable syringe technologies, reviewing and advancing sharps disposal technologies with Indian firms, and providing technical assistance to firms for the advancement of Uniject filling capacity.

Plans for the Future

With the conclusion of HealthTech III, limited funding for support from PATH Seattle for the PACT project is currently being provided through a direct cooperative agreement with USAID/India. Pending additional funding from USAID, PATH will continue to provide technical assistance to the PACT-CRH project and focus efforts on locating, screening, and transferring additional CRH products and technologies to Indian manufacturers.

C. Activities in Ukraine, USAID/Ukraine

Health Information Systems (HIS)/Ukraine

With field support funding that was added to the HealthTech agreement, the Ukraine Mission has been supporting the development and strengthening of a country-wide Health Information System (HIS) in Ukraine, focused primarily on immunization. By the end of HealthTech III, all oblasts (regions) were routinely submitting new reports on immunization practices, which are based on the reformed Health Management Information System (HMIS). The oblasts are increasingly using the information for making management decisions. PATH's ongoing, on-site training is regarded as a crucial means for strengthening local information management skills. The Ukrainian MOH used the new HMIS to develop its strategic multi-year immunization plan. This system was very useful in preparing Ukraine's application for GAVI assistance, which was submitted in January 2001.

In November 2000, PATH organized and conducted an international conference in Kyiv. The conference was attended by the chiefs of oblast pediatric and epidemiological services, key officials from the Ukrainian MOH, the National Center for Epidemiological Surveillance, and the Institute of Epidemiology, as well as by representatives of USAID, and delegations from Belarus, Moldova, and Georgia. Participants stressed the importance of the improved quality of data and its usefulness in management decision making, and praised PATH for its contribution to improved immunization program management, decreased vaccine wastage, reductions in contraindications, and the re-centralization of vaccine procurement in Ukraine. Regional adoption of the Ukraine HIS reforms developed under HealthTech was a key recommendation contained in the final report of the GAVI regional meeting held in St. Petersburg, Russia in June 2001.

Under separate funding, PATH is currently working with WHO/Euro and other GAVI partners in a program to introduce these information system reforms into other countries of the newly independent states and Eastern Europe, including Belarus, Moldova, and Georgia.

Ukraine Childhood Illness Project Coordination

Several other activities were funded by the Ukraine mission through this same mechanism, including coordination of the Ukraine Childhood Illness Project. Information linkages were established among three related projects—HIS, the Ukraine Birth Defects Program (UBDP), and the Chornobyl Childhood Illness Program (CCIP)—all directed at child health in Ukraine. A major goal of these three programs is to establish and/or strengthen health information and disease surveillance systems. Activity areas included:

- Provision of technical assistance to the CCIP and UBDP, based on experience gathered through the PATH Ukraine project to date.

- Establishment and maintenance of formal linkages among the three projects, which allows for the sharing of experience and the expertise from the various projects.
- Dissemination of information from the projects, including the organization of joint conferences.

The following specific subprojects were approved and implemented under this coordination effort:

- A small subgrant partially financed a nutritional education program of the Phenoketonuria (PKU), a family network in collaboration with the UBDP. These funds supported the organization by UBDP of a PKU Technical and Nutrition Education seminar for PKU parents, health care providers, and selected Ukrainian faculty from 18 oblasts of Ukraine and Kyiv City.
- An assessment of psychosocial support for families of children with spina bifida enabled a heightened awareness of the need for support to the families of children born with spina bifida. This cross-pollination of experience strengthened the sustainability of efforts toward building psychosocial support for patients and their families who face chronic medical needs.

Evaluation of Tuberculosis Test

A third activity under the Ukraine add-on to HealthTech was a local evaluation in Ukraine of the TB ICS test developed by HealthTech. PATH had already established a collaboration with the Institute of Pulmonology and Phthisiatry in Kyiv, where Professor Chernushenko had previously collected serum samples used in the initial optimization of the TB ICS test. In 2001, Professor Chernushenko agreed to conduct a prospective evaluation of the TB ICS test using serum collected from patients attending the TB clinic for TB diagnosis and treatment. The testing is being conducted on-site, as this will enable Professor Chernushenko to assess ease of use and acceptability of the test in addition to the clinical performance. To date, the study protocol has been developed, laboratory and patient enrollment procedures have been established, prototypes have been made, and human subjects protection committee applications have been submitted. The plan is for the study to commence under the follow on program—HealthTech IV.

A full report on all activities supported by the Ukraine Mission through field support funding under HealthTech has been submitted to the Mission.

Other Add-Ons

PATH was commissioned to provide services on the following projects through “add-ons” by other divisions and bureaus of USAID as noted.

D. SUSTAIN, USAID Bureau for Humanitarian Response (BHR)

Sharing U.S. Technology to Aid in the Improvement of Nutrition (SUSTAIN) is a program of PATH that is a highly innovative and successful volunteer organization whose goal is to improve the lives of the world's 800 million chronically malnourished people. The focus is on helping developing nations produce food products which are better, safer, more nutritious, and more affordable, especially for at-risk women and children. SUSTAIN acts as a partner in developing countries–working with businesses and the public sector–to identify specific ways that U.S. food-science technology can be effectively transferred.

In the last two years, USAID/BHR funded SUSTAIN, through an add-on to HealthTech, to conduct a study to assess the status of quality assurance technologies and systems used to improve the quality of PL 480 Title III Commodities. SUSTAIN assisted in a review and evaluation of the performance of

PL 480 commodity production plants in fortifying cereal products under the TQSA program and minimum micronutrient standards. A final report on this work was sent to USAID/BHR under separate cover.

E. Men and Reproductive Health Subcommittee of USAID's Interagency Gender Working Group, USAID Office of Population

Through an add-on to HealthTech, the Office of Population provided funding to support assistance to the Men and Reproductie Health Subcommittee for various activities that the committee wanted to undertake but had no mechanism to fund. This support facilitated PATH's participation in the subcommittee which is co-chaired by a PATH employee. The subcommittee focuses on current and emerging policy and program initiatives related to gender and the role of men in reproductive health. The three themes that were the focus of the committee's work were 1) adolescent and young men's reproductive health; 2) dual protection from a gender perspective (dual protection of barrier methods, especially condoms, for the prevention of unwanted pregnancy as well as STI/HIV/AIDS); and 3) gender-based violence, especially in the context of reproductive health services.

For example, a case study was implemented by the Society for the Integrated Development (SIDH) of the Himalayas in the District of Uttaranchal in Northern India. The case study documented SIDH's approach to working with adolescent and young men and women to improve reproductive health. SIDH has a unique experience in using culturally relevant issues of leadership and social justice to motivate young men to take more responsibility in the area of women's health. Similar projects, such as an effort to promote reproductive health awareness among men through peer educators by the K.E.M. Hospital Research Center in Pune, India, were also funded by this support, and have been reported on directly to the Office of Population.

F. Technical Assistance Activity on Vaccine Procurement, USAID/Armenia

In 1998 and 1999, the USAID Mission in Armenia provided field support funding through HealthTech to support the services of several PATH staff with expertise in procurement of vaccines to provide training on site in Armenia. A series of training visits were aimed at strengthening the ability of the Armenian government to obtain safe, effective vaccines at reasonable prices– particularly vaccines that are purchased outside of the UNICEF system. A report has been sent under separate cover to the USAID/Armenia mission.

G. AIDS Initiative Prevention Program (AIP) Phase II, USAID/Indonesia

Starting in 1997, the Indonesia Mission used field support through HealthTech to fund a local project in Indonesia that was conducted by PATH Indonesia. This Phase II project focused on Irian Jaya and expanded AIDS prevention programming that had been developed under the Phase I project that had been supported directly by the USAID mission. PATH designed the AIP to build capacity among the government agencies of Indonesia and indigenous NGOs to effectively develop targeted interventions for those at highest risk of HIV infection. Over the years, the project supported 14 NGOs and 4 government institutions in implementing 29 AIDS prevention programs that reached sex workers, port workers, gold miners, factory workers, and high school students. A comprehensive final report has been sent to the Indonesia Mission under separate cover.

Summary

In summary, health programs in developing countries face a number of problems related to inadequate or inappropriate technologies. For instance, existing technologies may be too expensive, too fragile, overly sensitive to heat and humidity, require highly-trained personnel, or are not targeted toward diseases of the developing world. Through the HealthTech: Technologies for Health program, USAID has invested in a means to address such problems with technology solutions to meet its stated Population Health and Nutrition goals. HealthTech has been a highly focused and successful program devoted to the development and introduction of a portfolio of health technologies that are applicable to the prevention and treatment of disease in the developing world. PATH has been pleased to offer its services and expertise in this area, and plans to continue this relationship through future programs and collaborations with USAID in years to come.

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HealthTech Private-Sector Collaborators
for the Advancement of Technology

Collaborator	Technology	Nature	Agreement
Diagnostic Technologies			
Abbott Laboratories (United States)	Syphilis ICS test	Introduction activities	Confidential disclosure (Active)
Accudx (United States)	Molecular diagnostics	Consulting	Consultant (Historical 12/1/00)
Advanced Microdevices (PVT) Ltd. (India)	Immunochromatographic (ICS) core technology	Licensing PATH technology	License (Active)
Behring Diagnostics (United States)	Gonorrhea/chlamydia monoclonal antibodies	Codevelopment	License (Active)
Biostar (United States)	Gonorrhea/chlamydia ICS test	Technical assistance	Confidential disclosure (Active)
Cape BioTech (South Africa)	Malaria ICS test	Technical assistance	Verbal (Active)
Christian Medical College (India)	Tuberculosis (TB) ICS test	Field-trial collaboration	To be determined
Contech Devices (India)	Pregnancy test	Technology transfer	License (Active)
Corixa Corporation (United States)	TB ICS test	Technology development	Collaboration (Active 4/1/01)
Egyptian Reference Diagnostic Center (ERDC) (Egypt)	Pregnancy ICS test	Technical assistance	None (Historical)
Human GmBH (Germany)	Malaria ICS test	Technology transfer	License (Potential)
J. Mitra & Co. Ltd. (India)	ICS core technology	Technology transfer	License (Active)
	Syphilis ICS test	Technology transfer	License (Active)
	Hepatitis B ICS test	Technology transfer	License (Active)
Lee Laboratories (United States)	Syphilis ICS test	Technology transfer	Confidential disclosure (Potential)
Mossman and Associates (United States)	TB dipstick	Technology transfer	License (Active)

Appendix 1

Collaborator	Technology	Nature	Agreement
Omega Diagnostics (United Kingdom)	Plasma separator card	Technology transfer	License (Active)
	Rotator	Technology transfer	License (Active)
	Solar recharger	Technology transfer	License (Active)
Orchid Biomedical (India)	TB ICS test	Technical assistance	None (Potential 4/1/01)
	Diphtheria ICS test	Technology transfer	License (Active)
	Syphilis ICS test	Technical assistance	Memorandum of Understanding (MOU) (Active)
	Malaria ICS test	Technical assistance	MOU (Active)
	Chlamydia ICS test	Technology transfer	License (Potential)
	ICS core technology	Technology transfer	License (Active)
Otsuka Pharmaceutical (Japan)	Collodial gold-core technology	Technology transfer	License (Active)
Pacific Biotech (Thailand)	HIV dipstick	Technology transfer	License (Active)
Public Health Laboratory Service (PHLS) (United Kingdom)	Diphtheria ICS test	Codevelopment	None (Active)
Premier Medical Corporation (PMC) (India)	ICS core technology	Technical assistance	None (Potential)
Quorum Diagnostics (Canada)	Syphilis ICS test	Technology transfer	License (Historical)
Sanguisep (Switzerland)	TB ICS test	Discussions	Confidential disclosure (Active)
SPAN Diagnostics (India)	Proteinuria test strip	Licensing PATH technology	License (Active)
	Syphilis ICS test	Technical assistance	None (Active)
	HIV dipstick	Technology transfer	License (Active)
	ICS core technology	Technology transfer	None (Active)
	Malaria ICS test	Technology transfer	License (Active)
Wiener Laboratories (Argentina)	HIV dipstick	Technology transfer	License (Active)

Collaborator	Technology	Nature	Agreement
Yayasan Hati Sehat (Indonesia)	ICS core technology	Technology transfer	License (Active 6/25/99)
	Hepatitis B ICS test	Technology transfer	License (Active)
	HIV dipstick	Technology transfer	License (Active)
Hardware Technologies			
MCH Products (Nepal)	Delivery kit	Technical assistance	Collaboration (Active 4/1/01)
MedTech (India)	Female condom	Collaboration	(Active)
O'Ryan Industries (United States)	AviScope™	Codevelopment	Confidential disclosure (Active)
Polynor (Norway)	Sharps disposal box	Technical assistance	None (Active)
Safe Injection Technologies			
Aplicaciones Farmaceuticas (Mexico)	Uniject™ - Cyclofem®	Technical assistance	None (Potential)
	Uniject - oxytocin	Technical collaboration	None (Potential)
BD (Becton Dickinson) (United States)	SoloShot™	Licensing PATH technology	License (Active)
	Disposal boxes	Codevelopment	None (Potential)
	Uniject	Licensing PATH technology	License (Active)
Bharat Biotech (India)	Uniject – hepatitis B	Technical assistance	None (Active)
Chemi Automatics Design Bureau (Russia)	Jet injector	Technical assistance	MOU (Active)
Commonwealth Serum Laboratories Limited (Australia)	Uniject – TT, DTP, influenza vaccine	Collaborator	Confidential disclosure (Active)
Eastbridge Limited (United Kingdom)	Jet injector	Codevelopment	Confidential disclosure (Potential)
Famy Care (India)	Uniject	Technology transfer	None (Potential)
Felton Medical, Inc. (United States)	Jet injector	Codevelopment	Confidential disclosure (Potential)

Appendix 1

Collaborator	Technology	Nature	Agreement
Gedeon Richter (Hungary)	Uniject - oxytocin	Collaborator	None (Historical)
Horizon Medical (United States)	Uniject	Technology transfer	(Historical)
Integrated Environmental Technologies (United States)	Medical waste	Technical assistance	Technical Services (Active)
Greencross Vaccine Corporation (Korea)	Uniject – hepatitis B	Technical collaboration	None (Historical)
Medtechnologia (Russia)	MEDiVAX™ jet injector	Codevelopment	License (Historical)
Pharmacia & Upjohn (United States)	Uniject	Fill with DMPA	None (Potential)
Prismedical (United States)	Measles vaccine reconstitution timer (MVR)	Technical assistance	Technical Services (Active)
P.T. Bio Farma (Indonesia)	Uniject - hepatitis B	Technical assistance	Partnership Agreement (Active)
	Uniject – TT	Technical assistance	Partnership Agreement (Active)
Shantha Biotechnics Pvt. Ltd. (India)	Uniject – hepatitis B	Technical assistance	None (Active)
Statens Seruminstitut (Denmark)	Uniject – TT	Technical collaboration	Confidential disclosure (Historical)
Universal Preservation Technologies (United States)	Vaccine reconstitution device	Codevelopment	Collaboration (Potential)
Vitajet (Brazil)	MEDiVAX Jet injector	Field-trial collaboration	License (Historical)
Vaccine Temperature Management			
3M Company (United States)	Freeze indicators	Codevelopment	None (Historical)
CCL Label (United States)	Vaccine vial monitors (VVMs)	Technical assistance	None (Historical)
LifeLines (United States)	VVMs	Codevelopment	None (Active)
LisaLines (India)	VVMs	Technical collaboration	None (Active)
Serum Institute of India (India)	VVMs	Technical collaboration	MOU (Active)
Thermal Systems (United States)	Refrigerator/cold box	Technical assistance	None (Active)

HealthTech Public-Sector Collaborators
for the Advancement of Technology

Collaborator	Technology	Nature	Description
Multiple Technologies			
ICICI and USAID Mission (India)	Miscellaneous	Funding	Under PACT-CRH and field support to HT, USAID India has supported development, technology transfer activities, and introduction of: syphilis ICS, malaria ICS, tuberculosis ICS, gonorrhea ICS, and chlamydia ICS tests; medical waste (needle puller); and DMPA in Uniject.
Diagnostic Technologies			
British Columbia Center for Disease Control (Canada)	Gonorrhea (GC) immunochromato-graphic strip (ICS) test	Evaluation	Validation of GC ICS tests.
Center for AIDS and STDs – University of Wash. (United States)	Other diagnostics	Collaboration	MOU signed to collaborate on the introduction of rapid diagnostics in the developing world.
Centers for Disease Control and Prevention (United States)	GC ICS test	Evaluation	Testing of GC ICS samples.
	Chlamydia ICS test	Evaluation	Testing of Chlamydia ICS samples.
	Syphilis ICS test	Evaluation	Worked with CDC to validate ICS test on serum specimens from South Africa.
	Syphilis rapid test	Collaboration	Held Rapid Syphilis Test meeting to discuss FDA-approval process.
Christian Medical College (India)	Tuberculosis (TB) ICS test	Field-trial collaboration	Discussing 2001 field trial of TB ICS test.
DeKalb County STD Clinic (United States)	GC ICS test	Evaluation	Provide testing of GC ICS.
Egyptian Reference Diagnostic Center (Egypt)	ICS core technology	Funder	The USAID mission in Egypt provided funding for transfer of the ICS core technology to ERDC.
	Schistosomiasis Vaccine	Administrative management	USAID commissioned PATH as the technical and administrative management contractor for SVDP.
Georgetown University (United States)	Malaria ICS test	Licensing intellectual property	PATH signed agreement to license HRP2 Mabs. Ends 12/09.

Collaborator	Technology	Nature	Description
Helen Keller International (Indonesia)	Vitamin A enzyme immunoassay (EIA) test	Field-trial collaboration	Support for field test of vitamin A EIA and ICS tests.
Horizons (United States)	Syphilis rapid test	Operations research	Concept paper on research using rapid syphilis test in antenatal programs.
Institute of Nutrition of Central America & Panama (Guatemala)	Vitamin A EIA test	Field-trial collaboration	Support for field test in Guatemala and Nicaragua.
International Science and Technology Institute (MOST) (United States)	Vitamin A EIA test	Field-trial collaboration	Field trials of vitamin A EIA test in Nicaragua and Guatemala under USAID-funded MOST project.
Kyiv TB Research Institute (Ukraine)	TB ICS test	Field-trial collaboration	The TB Research Institute supported initial research and sample collection for the TB ICS test. Funding has been received to move forward with a field trial for the ICS test in 2001.
Karolinska Institute (Sweden)	Uniject – oxytocin	Field trial evaluation	Institute conducted independent trials of Uniject.
	Uniject -prostaglandin	Field trial evaluation	Institute conducted independent trials of Uniject.
Ministry of Health - Madagascar (Madagascar)	Vitamin A EIA test	Technical assistance	Provided training on vitamin A EIA test for micronutrient survey in 1999.
MNH (Maternal and Neonatal Health) (United States)	Syphilis ICS test	Field-trial collaboration	Task order is pending for the introduction of the syphilis ICS in rural Peru.
National Institutes of Health (NIH), Office of Technology Transfer (United States)	Malaria ICS test	Licensing intellectual property	Signed 2/98. License for malaria antibody.
NGO Networks (United States)	Syphilis rapid test	Operations research	Prepared collaboration in Malawi.
Royal Institute for Tropical Medicine (Netherlands)	DTP diagnostics	Discussions; possible collaborations	Discussions on future diagnostic activities underway.

Collaborator	Technology	Nature	Description
South African Institute of Medical Research (SAIMR) (South Africa)	GC ICS test	Field-trial collaboration	Potential field-test site and support of introduction activities.
	Chlamydia ICS test	Field-trial collaboration	Potential field-test site and support of introduction activities.
University Peruana Cayetano Heredia (Peru)	Syphilis ICS test	Field-trial collaboration	The university assisted with the field testing of the rapid syphilis test in rural Peru.
University of Massachusetts (United States)	Vitamin A ICS test	Licensing intellectual property	University is owner of RBP antibodies intellectual property.
University Research Center (United States)	Malaria ICS test	Collaboration	Field testing and introduction support for malaria diagnostic test.
WHO (Switzerland)	Malaria ICS test	Introduction support	WHO is supporting rapid malaria test introduction activities.
	Other diagnostics	Introduction	STD Diagnostics Initiative - PATH is an active member.
	HIV dipstick	Introduction	PATH is a WHO Collaborating Center on AIDS.
Hardware Technologies			
Ministry of Health (Tanzania)	Delivery kit	Field-trial collaboration	A field evaluation of the delivery kit is planned in Tanzania in 2001.
Save the Children (Nepal)	Delivery kit	Technical assistance	Set up local safe birth delivery kit project.
The Concept Foundation (Thailand)	Miscellaneous	Collaboration	Concept licenses Cyclofem® for use in Uniject.
WHO (Switzerland)	Medical waste	Collaboration	Member of Healthcare Waste Working Group.
Safe Injection Technologies			
BASICS (United States)	Vaccine vial monitors (VVMs) and auto-disable syringes	Collaboration	Interacted on multiple safe injection topics.
Bolivian Ministry of Health (Bolivia)	Uniject	Field-trial collaboration	Implemented Uniject field trials.

Collaborator	Technology	Nature	Description
GAVI (France)	Safe injection	Collaboration	Collaboration with field evaluations and advancement activities for appropriate safe injection technologies.
Indonesian Ministry of Health (Indonesia)	Uniject-oxytocin	Field-trial collaboration	Implemented Uniject field trials.
	Uniject-tetanus toxoid	Field-trial collaboration	Implemented Uniject field trials.
	Uniject-hepatitis B	Field-trial collaboration	Implemented Uniject field trials introducing hepatitis B vaccine in Uniject.
Macfarlane Burnet Centre for Medical Research (Australia)	Uniject-hepatitis B	Lab testing	Conducted independent laboratory testing of Uniject.
Pan American Health Organization (Bolivia)	Uniject	Field-trial collaboration	Oversaw Uniject introductions in Bolivia.
Statens Bakteriologiska Laboratorium (Sweden)	Uniject	Technical collaboration	Provided assistance with testing Uniject with various medicaments.
USAID Office of Population Cooperating Agencies	Safe injection	Collaboration	Through USAID, PATH is working with a group of Office of Population cooperating agencies to advance the introduction of auto-disable syringes and safety boxes with DMPA.
UNICEF (United States)	Uniject	Collaboration	Partnership for Child Health.
	Safe injection	Collaboration	Collaboration with field evaluations and advancement of appropriate technologies, including TT in Uniject.
University of Virginia (United States)	Safe injection	Collaboration	Shared information on protection from needlestick injuries.
Village Reach (Mozambique)	Vaccine delivery systems	Collaboration	Provided technical assistance for start of model program demonstrating systems for managing delivery of vaccines.
WHO (Switzerland)	Safe injection	Collaboration	Collaboration with field evaluation and advancement of appropriate safe injection technologies. Safe Injection Global Network.
	Uniject	Collaboration	Policy and review of technical issues.

Collaborator	Technology	Nature	Description
Vaccine Temperature Management			
Collaborative Center for Cold Chain Management (South Africa)	VVMs	Field-trial collaboration	Conducted study of VVMs in use.
GAVI (France)	VVMs	Collaboration	Collaboration with field evaluations and advancement activities for appropriate safe injection technologies.
REACH (John Snow, Inc.) (United States)	Cold box	Field study	Assessment of cold-box technologies.
UNICEF (United States)	VVMs	Introduction support	Collaboration with field evaluations and advancement of appropriate technologies. UNICEF has mandated that VVMs be placed on all vaccines by 2001.
WHO (Switzerland)	VVMs	Collaboration	WHO and PATH have collaborated on introduction and training strategies since 1990. Training and introduction materials were produced in 1995 and revised in 1999.
WHO/AFRO (Africa)	VVMs	Training	Developing training materials and curriculum on vaccine management for EPI workers in African countries.

HealthTech Country Activities
for Technology Advancement Outside the United States

Country	Technology	Activity	Collaborator(s)
Angola	Uniject - oxytocin	Field evaluation/trials	WHO, Karolinska Institute
Argentina	HIV dipstick test kit	Technology transfer	Wiener Laboratories
	Vaccine vial monitors	Field evaluation/trials	MOH
Armenia	Vaccine procurement	Technical assistance	MOH
Australia	Uniject - TT, DTP, influenza vaccine	Technical assistance	Commonwealth Serum Laboratories Limited
	Uniject - hepatitis B	Lab testing	Macfarlane Burnet Centre for Medical Research
Bangladesh	Delivery kit	Introduction activities	
	Steam sterilizer	Field assessment	Engender Health
	Vaccine vial monitors	Field evaluation/trials	Local healthcare workers
Bhutan	Vaccine vial monitors	Post-introduction trial	WHO
Bolivia	MEDiVAX™ jet injector	Field evaluation/trials	
	Uniject - TT	Field evaluation/trials	MOH, Pan American Health Organization (PAHO)
	Vaccine vial monitors	Field evaluation/trials	Local healthcare workers
Botswana	Immunochromatographic (ICS) test for tuberculosis	Field evaluation/trials	Centers for Disease Control and Prevention
Brazil	MEDiVAX	Technical development	Vitajet
	SoloShot™	Technical assistance/training	
	Vaccine vial monitors	Field evaluation/trials	MOH, PAHO
Burkina Faso	Uniject - TT	Introduction	Partnership for Child Health
Cameroon	Vaccine vial monitors	Field evaluation/trials	Local healthcare workers
Canada	ICS test for gonorrhea	Field evaluation/trials	British Columbia Centre for Disease Control
	ICS test for malaria	Evaluation	University of Toronto
	ICS test for syphilis	Technology transfer	Quorum Diagnostics
China	SoloShot	Field evaluation/trials	

Country	Technology	Activity	Collaborator(s)
Czech Republic	ICS test for syphilis	Field evaluation/trials	National Reference Laboratory of Diagnostic Syphilis and Demotoveneric Diseases
Denmark	Uniject - TT	Technical collaboration	Statens Seruminstitut
Dominican Republic	ICS test for syphilis	Field evaluation/trials	
Egypt	BIRTHweigh II™	Technical collaboration/ Technology transfer	
	ICS test for pregnancy	Technology transfer	Egyptian Reference Diagnostic Center
	Schistosomiasis vaccine	Technology development	Egyptian Reference Diagnostic Center
	MEDiVAX	Field evaluation/trials	MOH, WHO
	Uniject - prostaglandin	Field evaluation/trials	Karolinska Institute
	Vaccine vial monitors	Field evaluation/trials	
Ethiopia	Vaccine vial monitors	Training assistance	WHO, MOH
Germany	ICS falciparum malaria test	Technology transfer	Human GmBH
	RBP-EIA (vitamin A test)	Technology transfer	TBD
Guatemala	MEDiVAX	Field evaluation/trials	
	RBP-EIA (vitamin A test)	Field evaluation/trials	Institute of Nutrition of Central America & Panama
Hungary	Uniject - oxytocin	Technical collaboration	Gedeon Richter
India	AviScope™	Field evaluation/trials	International Agency for Research on Cancer
	Delivery kit	Regional workshop	
	HIV dipstick test kit	Technology transfer	SPAN Diagnostics
	ICS core technology	Technology transfer	Orchid Biomedical
	ICS core technology	Technology transfer	J. Mitra & Co. Ltd.
	ICS core technology	Technology transfer	Advanced Microdevices (PVT) Ltd.
	ICS core technology	Technology transfer	SPAN Diagnostics

Country	Technology	Activity	Collaborator(s)
India, cont.	ICS core technology	Technology transfer	Premier Medical Corporation
	ICS falciparum malaria test	Technical assistance/training	Orchid Biomedical
	ICS falciparum malaria test	Technology transfer	SPAN Diagnostics
	ICS test for diphtheria	Technology transfer	Orchid Biomedical
	ICS test for hepatitis B	Technology transfer	J. Mitra & Co. Ltd.
	ICS test for pregnancy	Technology transfer	Contech Devices
	ICS test for syphilis	Technical assistance	Orchid Biomedical
	ICS test for syphilis	Technology transfer	J. Mitra & Co. Ltd.
	ICS test for tuberculosis	Field evaluation/trials	Christian Medical College
	Proteinuria test strip	Technology transfer	SPAN Diagnostics
	Rapid test for syphilis	Technology assistance	SPAN Diagnostics
	Safe medical waste disposal	Field evaluation/trials	Srishti
	Safe medical waste disposal	Technical collaboration	Medikits
	SoloShot	Field evaluation/trials	
	Uniject	Technical assistance/training	Famy Care
	Uniject - hepatitis B	Technical assistance/training	Shantha Biotechnics
	Uniject - hepatitis B	Technical assistance/training	Bharat Biotech
	Uniject - prostaglandin	Field evaluation/trials	Astra-IDL Limited
	Vaccine vial monitors	Technical assistance	Serum Institute of India, LisaLines
Indonesia	BIRTHweigh II™	Introduction	MOH in Healthy Start Program
	HIV dipstick test kit	Technology transfer	Yayasan Hati Sehat
	ICS core technology	Technology transfer	Yayasan Hati Sehat
	ICS test for hepatitis B	Technology transfer	Yayasan Hati Sehat
	ICS test for tuberculosis	Field evaluation/trials	Mataram General Hospital
	MEDiVAX	Field evaluation/trials	
	RBP-EIA (vitamin A test)	Field evaluation/trials	Helen Keller International
	Safe medical waste disposal	Field evaluation/trials	
	SoloShot	Field evaluation/trials	MOH

Country	Technology	Activity	Collaborator(s)
Indonesia, cont.	Uniject - TT	Technical collaboration	P.T. Bio Farma
	Uniject - hepatitis B	Field evaluation/trials	MOH
	Uniject - hepatitis B	Introduction	MOH
	Uniject - hepatitis B	Technical collaboration	P.T. Bio Farma
	Uniject - oxytocin	Field evaluation/trials	MOH, WHO
	Uniject - TT	Field evaluation/trials	MOH
	Vaccine vial monitors	Field evaluation/trials	MOH
Irian Jaya	AIDS Initiatives in Irian Jaya	Field support to HT	Local NGOs
Japan	Colloidal gold-core technology	Technology transfer	Otsuka Pharmaceutical
Kenya	Delivery kit	Technical assistance/training	
	AviScope	Field evaluation	Alliance for Cervical Cancer
	ICS test for syphilis	Field evaluation/trials	
	Vaccine vial monitors	Field evaluation/trials	MOH, WHO
Latvia	ICS test for diphtheria	Field evaluation/trials	Public Health Laboratory Services (PHLS)
Madagascar	RBP-EIA (vitamin A test)	Technical assistance/training	MOST
Malawi	BIRTHweigh II	Technical collaboration	
	ICS falciparum malaria test	Field evaluation/trials	CDC
	ICS test for syphilis	Field evaluation/trials	NGO Networks
Mali	Uniject - TT	Introduction	Partnership for Child Health
Mexico	AviScope	Field evaluation/trials	
	ICS test for syphilis	Field evaluation/trials	NIH/Mexico
	Uniject - Cyclofem®	Technical collaboration	Aplicaciones Farmaceuticas
	Uniject - oxytocin	Technical collaboration	Aplicaciones Farmaceuticas
	Vaccine vial monitors	Field evaluation/trials	MOH, and others
Mozambique	ICS test for syphilis	Field evaluation/trials	
	Vaccine cold chain services	Collaboration	Village Reach
Nepal	Clean Home Delivery Kit	Technical assistance	Save the Children
	Clean Home Delivery Kit	Introduction activities	MCH Products

Country	Technology	Activity	Collaborator(s)
Nepal, cont.	Vaccine vial monitors	Field evaluation/trials	MOH, WHO
Netherlands	Diagnostics	Collaboration	Research Institute for Tropical Medicine
Nicaragua	RBP-EIA (vitamin A test)	Field evaluation/trials	MOST/CDC
Norway	Sharps disposal box	Technical collaboration	Polynor AS
Pakistan	SoloShot	Field evaluation/trials	
	Vaccine vial monitors	Field evaluation/trials	MOH, WHO
Peru	ICS falciparum malaria test	Field evaluation/trials	CDC, NAMRU
	ICS test for syphilis	Field evaluation/trials	University Peruana Cayetano Heredia
	Safe medical waste disposal	Field evaluation/trials	
	Vaccine vial monitors	Field evaluation/trials	MOH, WHO
Philippines	Vaccine vial monitors	Field evaluation/trials	MOH and other
Russia	MEDiVAX	Field evaluation/trials	Medtechnologia
	Cold box	Field study	REACH (John Snow, Inc.)
	Needle-free injection systems	Technical assistance/training	Chemi Automatics Design Bureau
Sierra Leone	Vaccine vial monitors	Field evaluation/trials	MOH, Canadian Public Health Association (CPHA)
Singapore	Uniject blanks	Technology transfer	BD
South Africa	Female condom	Field evaluation/trials	Addington Hospital
	HIV dipstick test kit	Field evaluation/trials	MCDI
	ICS falciparum malaria test	Technical assistance/training	Cape Biotech
	ICS Test for chlamydia	Field evaluation/trials	South African Institute of Medical Research (SAIMR)
	ICS test for gonorrhea	Field evaluation/trials	South African Institute of Medical Research (SAIMR)
	AviScope	Field evaluation	Engender Health
	Safe medical waste disposal	Field evaluation/trials	
	Vaccine vial monitors	Field evaluation/trials	Collaborative Center for Cold Chain Management
Switzerland	HIV dipstick test kit	Collaboration	WHO
	ICS test for tuberculosis	Collaboration	Sanguisep

Country	Technology	Activity	Collaborator(s)
Switzerland, cont.	STD diagnostics	Collaboration	STD Diagnostics Initiative
	Immunization technologies	Collaboration	GAVI
	Safe injection technologies	Collaboration	WHO
	Vaccine vial monitors	Introduction activities	WHO
Tanzania	Delivery kit	Field evaluation/trials	National Institute of Medical Research
	Vaccine vial monitors	Field evaluation/trials	
Thailand	HIV dipstick test kit	Field evaluation/trials	
	HIV dipstick test kit	Licensed PATH technology	The Concept Foundation
	HIV dipstick test kit	Technology transfer	Pacific Biotech
	Vaccine vial monitors	Field evaluation/trials	MOH
Uganda	ICS test for tuberculosis	Field evaluation/trials	Case Western Station
Ukraine	ICS test for diphtheria	Field evaluation/trials	PHLS
	ICS test for syphilis	Field evaluation/trials	
	ICS test for syphilis	Introduction activities	
	ICS test for tuberculosis	Field evaluation/trials	Kyiv TB Research Institute
United Kingdom	Plasma separator card	Technology transfer	Omega Diagnostics
	Rotator	Technology transfer	Omega Diagnostics
	Solar recharger	Technology transfer	Omega Diagnostics
	ICS test for diphtheria	Collaboration	(PHLS)
	Uniject – Cyclofem	Technical collaboration/ lab study	University of Warwick
Vietnam	ICS test for syphilis	Field evaluation/trials	
	Vaccine vial monitors	Field evaluation/trials	
Yemen	Vaccine vial monitors	Field evaluation/trials	MOH, WHO
Yugoslavia	Vaccine vial monitors	Technology transfer	
Zambia	Vaccine vial monitors	Field evaluation/trials	MOH, Canadian International Development Agency

Country	Technology	Activity	Collaborator(s)
Zimbabwe	ICS Test for chlamydia	Field evaluation/trials	Battelle/Seattle Research Center
	ICS test for gonorrhea	Field evaluation/trials	Battelle/Seattle Research Center
	ICS test for tuberculosis	Field evaluation/trials	University of Zimbabwe
	Proteinuria test strip	Technology transfer	McDonald Scientific
	Vaccine vial monitors	Field evaluation/trials	MOH, WHO, CPHA

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3. Drain PK, Holmes KK, Hughes JP, Koutsky LA. **Determinants of cervical cancer in developing countries.** *International Journal of Cancer* in press. Presented in part as a panel discussion at the *2001 Global Health Council Conference* "Healthy Women, Healthy World: Challenges for the Future," May 31, 2001.

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5. Horton S, Levin CE. Commentary on **Evidence That Iron Deficiency Anemia Causes Reduced Work Capacity.** *Nutrition*. 131(2S-II), February 2001.

6. Sutanto A, Nelson CM, Stewart T, Widjaya A, Otto B, Muller N**,** Stott V, Gunawan N. **Bringing child survival to the community: birth-centered outreach in Indonesia**. *Bull World Health Organ*, in press.

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