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path
Program for Appropriate Technology in Health

October 30, 2002

Dr. Tore Godal
Global Alliance for Vaccines and Immunization
c/o UNICEF
Palais des Nations
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Dear Tore:

Now that major partners in the immunization and health fields have come together through GAVI, we have the opportunity to move away from "business as usual" in developing and introducing vaccines for resource-poor countries. The Accelerated Development and Introduction Plan (ADIP) model introduces a new paradigm for action in the public sector. This paradigm requires active participation from industry and a dedicated and dynamic staff to achieve a common measurable public health endpoint. The GAVI Board's articulation and funding of the ADIP concept provides the opportunity–and the challenge–to dramatically transform vaccine development and introduction for the poorest children in the world through creative and rigorous public-/private-sector collaborations.

PATH is excited to have an opportunity to work with GAVI to take the rotavirus vaccine agenda forward. The attached proposal from PATH emphasizes a solid partnership with a balanced agenda and a strong team to lead the initiative. A particularly strong aspect of our proposal is the substantive involvement of three Primary Strategic Partners: the World Health Organization, the United States Centers for Disease Control and Prevention, and the Children's Vaccine Program at PATH. The project leaders mirror this concept of balance, partnership, and strength. Director John Wecker, Ph.D., has extensive experience with the pharmaceutical industry and public/private partnerships; and Scientific Director Roger Glass, M.D., Ph.D., has a proven track record of scientific excellence and has long been the champion of rotavirus vaccine. The development and introduction of rotavirus vaccines will be a dynamic process of constant evaluation and adjustment as new information unfolds through work with GAVI, the public sector, and industry to find the solutions that will best serve the developing world. As the president of PATH, I would like to take this opportunity to confirm our enthusiastic support and the commitment of the organization at its highest levels for the success of the Rotavirus ADIP team.

We look forward to discussing our proposal with you at the earliest opportunity. We stand ready to take this agenda forward without delay and eagerly await the decision of the GAVI proposal review group.

With best regards,

Christopher J. Elias, M.D., M.P.H.
President

CE:ju
Attachment

Accelerated Development and Introduction Plan (ADIP) for Rotavirus Vaccines

A Final Revised Proposal to GAVI

Submitted by
Program for Appropriate Technology in Health (PATH)

In collaboration with
the United States Centers for Disease Control and Prevention and
the World Health Organization

January 2003

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Executive Summary

The Accelerated Development and Introduction Plan (ADIP) for Rotavirus Vaccines provides an opportunity to expedite the availability of rotavirus vaccines into countries where they are needed most. Program for Appropriate Technology in Health (PATH) proposes to host the ADIP, as we are an active participant in the rotavirus community and have already made significant contributions to move the agenda forward. In addition, PATH currently hosts several projects with a similar charge to accelerate the development of neglected vaccines, and through our Children's Vaccine Program (CVP), we have been an active partner in GAVI and the formation of The Vaccine Fund. The depth and breadth of our experience make PATH a sound host for the ADIP for Rotavirus Vaccines.

The ADIP team we have assembled reflects a new model for public/private partnership. It is made up of enthusiastic, experienced, capable, and diverse individuals who can develop a vaccine and introduce it to the developing world. The ADIP will become a new Strategic Program within PATH's organizational structure and will be led by Director Dr. John Wecker, a leader with significant pharmaceutical industry experience who has previously worked with public/private partnerships from the industry side. His experience will help guide the team in the best and most efficient ways to work with the private sector, while also addressing the public sector's interest in the vaccination needs of the developing world. Scientific Director Dr. Roger Glass will bring public health experience and scientific rigor to the agenda with a dynamic enthusiasm for his work in rotavirus. The ADIP team will also include dedicated staff members from two Primary Strategic Partners (the Children's Vaccine Program and the Centers for Disease Control and Prevention), with a liaison from the third Primary Strategic Partner, the World Health Organization (WHO). This team constitutes a powerful group with substantive involvement from major partners to lead the rotavirus agenda ahead.

The ADIP for Rotavirus Vaccines has been created to compress the time line to vaccine availability by building off of the framework of present activities and directing the way to vaccine introduction. The plan is structured around three strategic areas: Establishing Value, Communicating Value, and Delivering Value. The plan is designed to be flexible, creative, and catalytic. By having a full-time staff, we can focus on compiling information for advocacy, creating messaging for decision makers, and working with the global community to engender support for rotavirus vaccination. All of these activities will be coordinated with industry and vetted with the GAVI ADIP Steering Committee and with input from the Technical Review and Advisory Committee to speed vaccine delivery to those most in need.

PATH offers significant technical expertise to the ADIP team as host and as partner. PATH is a leader in the field of public/private partnership, with a cross-program Business Development and Commercialization Group that works on a range of topics from vaccine development and immunization technologies to laboratory diagnostics. PATH also has experience with vaccine introduction, evaluation, training, surveillance and disease burden studies, behavior change, demand forecasting, and cost-effectiveness evaluations. In this rich environment, PATH remains nimble, with the ability to work with multiple partners and create flexible working relationships to enhance each partner's varying strengths. Administratively, PATH has the ability to hire highly qualified staff quickly, negotiate milestone-driven agreements with industry, arrange travel and meetings on short notice, and work within a project milestone framework. In addition to these skills and

characteristics, PATH will offer support to the ADIP by providing staff time to cover team member responsibilities during the start-up phase until the permanent team is in place. CVP will continue its work in rotavirus prevention with surveillance and disease burden projects and vaccine development efforts. As a Primary Strategic Partner, CVP will also contribute one position to the ADIP team.

The attached proposal outlines PATH's experience and the partnerships required to make this project successful. PATH will work to actively support the ADIP process with the full support of PATH's president and management.

I. Introduction

One key objective of the Global Alliance for Vaccines and Immunization (GAVI) is to accelerate the development and introduction of priority vaccines into developing countries. A tragic inequity exists in the developing world, where children often receive vaccines a full 15 to 20 years after children in wealthier countries. Streptococcus pneumonia and rotavirus infections, which together kill nearly 2 million children each year, have been identified as GAVI priorities. In June 2002, the GAVI Board approved the formation of Accelerated Development and Introduction Plans (ADIPs) for Pneumococcal Conjugate and Rotavirus Vaccines. The ADIPs are designed to correct the inequity in vaccine access by coordinating and advancing the work of public and private sectors towards an ultimate goal of accelerating the introduction of pneumococcal and rotavirus vaccines into developing countries.

Rotavirus is the most common cause of severe dehydrating diarrhea among children worldwide. Approximately 500,000 deaths from rotavirus occur each year among children under five years of age, and 85 percent of these deaths occur in the poorest countries. In both developed and developing countries, rotavirus is the most frequent cause of severe diarrhea and accounts for 30 to 60 percent of all hospitalizations for childhood diarrhea. The fact that rotavirus infection occurs almost universally among children in both developed and developing countries suggests that improvements in sanitation and hygiene are unlikely to have any impact on the incidence of the disease. While rotavirus diarrhea can usually be treated with oral rehydration, children with severe illness experience vomiting and dehydration, which make simple oral rehydration difficult. These children require higher levels of care, which are often unavailable. Where access to care is limited, mortality is highest and the effectiveness of oral rehydration solution programs may not be sufficient.

Vaccines against rotavirus have been recommended by the international community as the best hope for prevention of rotavirus-related diarrheal deaths and morbidity. A variety of live, oral rotavirus vaccines are either currently licensed (China) or in late stages of development, and some of these vaccines will likely be available for introduction into immunization programs within the next four to five years. If these vaccines are to be introduced in the developing world without delay, there must be a clear, coordinated plan to make this happen. This plan must support activities to expedite the development, evaluation, and use of rotavirus vaccines in routine immunization programs, and it must have the full support and cooperation of both the public and private sectors. The ADIP provides the structure for such a plan.

As described in more detail below, Program for Appropriate Technology in Health (PATH) is uniquely qualified to host the rotavirus ADIP team. PATH currently manages a US$245 million portfolio of vaccine development and introduction programs, including the US$50 million Malaria Vaccine Initiative (MVI), the US$70 million Meningitis Vaccine Project (MVP) in partnership with the World Health Organization (WHO), and the US$125 million Children's Vaccine Program (CVP). In fact, rotavirus vaccine has been a key program area for CVP, and our surveillance and vaccine development activities have already provided a platform for the ADIP and will continue to support it.

All these programs are managed at PATH within a team framework that emphasizes independent decision making and encompasses collaborative interactions with major international and multilateral partners. PATH has demonstrated its ability to recruit and retain senior managers from industry and to successfully manage the creative tension between technical, public health, and business perspectives. In addition, PATH has the ability to form and manage productive alliances with a long-term view toward programmatic success. PATH's robust financial management systems, our proven ability to organize and stage global meetings, our institutional comfort in making decisions that involve risk, and our extensive experience with grants management will help us successfully manage and implement the ADIP.

II. Proposed Vision and Strategy for the ADIP for Rotavirus Vaccines

The long-term objective for the ADIP for Rotavirus Vaccines is to introduce a safe and effective rotavirus vaccine through a sustainable Expanded Program on Immunization (EPI) to children in developing countries. By focusing on activities that will create a predictable demand and ensure adequate supply of vaccine, we hope to accelerate vaccine introduction and uptake. In order to ensure demand, consumers (countries) must be aware of their need for a product and be willing to purchase it. In order to ensure supply, industry must be aware of the demand for a product and be assured that the product will be purchased before it will commit resources toward production. The ADIP will support or promote a variety of specific activities towards these ends, within a coordinated programmatic agenda, including vaccine development, advocacy, demand estimation, and coordination with partners and stakeholders. Only those activities that explicitly and clearly move countries toward vaccine introduction will be contained within the ADIP. An essential piece of the ADIP is a dedicated staff with the leadership, drive, and expertise to coordinate and lead the community to accelerate the availability of this lifesaving vaccine in the developing world.

A. Partnering With Other Stakeholders

It is important to understand that the current three-year ADIP grant will be a catalyst to accelerate rotavirus vaccine availability; however, the ADIP will begin within a rich environment of activities already underway and will comprise one part of the universe of activities that support rotavirus vaccine development. A variety of stakeholders have been working to gather data for decision making, conduct basic science research, and advocate for and develop vaccines. To be most successful, the ADIP will have to coordinate its agenda with all partners and their existing or planned activities, yet not be reluctant to take the lead and bring partners along to move the agenda forward.

The ADIP will add value to current activities related to rotavirus vaccine evaluation and introduction in two ways. First, to maximize efficiency, the ADIP team will coordinate its activities with those underway or planned by other groups into a broader overall vision. In this way, limited funds are first allocated to critical-path activities and each stakeholder is aware of the work of others. Second, the ADIP will provide a mechanism to support critical, but currently unsupported, activities that can accelerate vaccine availability. In the context of these distinct but complementary roles, we will refer to two agendas of activities: the Rotavirus Action Plan (RAP) and the ADIP for Rotavirus Vaccines. The RAP refers to the larger universe of activities (including ADIP-related and non-ADIP-related activities) relating to the rotavirus vaccine that, taken together, will promote early introduction. The

ADIP for Rotavirus Vaccines refers to the group of activities that are directly supported and conducted by the ADIP team and comprises the bulk of this proposal.

B. The Rotavirus Action Plan (RAP)

The RAP was put together to help organize the ADIP for Rotavirus Vaccines. The RAP shows the activities along with the timelines that are necessary to move the rotavirus agenda forward. It was developed from an endpoint of 80 percent vaccine coverage to the present day, listing all anticipated tasks necessary to meet the goal. These tasks were referenced to other vaccine introduction plans and were modified according to anticipated milestones of vaccine development.

The RAP includes activities of many groups currently working to expedite rotavirus vaccine development and introduction, including industry, public-sector agencies, ministries of health, and academia. The ADIP team developed the RAP so that all ADIP activities could integrate seamlessly within the framework of ongoing and future projects by other partners. By referring to the RAP, the ADIP team will obligate its resources to activities that reduce the time necessary to make rotavirus vaccine available in the developing world.

While the ADIP is a key component of the RAP, the work of the other groups is vital. The ADIP should neither inhibit their work nor replace funding provided by them. Instead, it should enhance the work by incorporating it into a comprehensive plan. The ADIP should play a principal role in coordinating, and in some cases leading, activities to the common endpoint of vaccine introduction. By helping to ensure that the tasks of the various stakeholders are focused on achieving the short- and long-term objectives of ADIP, we can multiply the effect of ADIP funds.

C. The ADIP for Rotavirus Vaccines

The ADIP team will support and coordinate a range of specific, outcome-based activities for which it is principally responsible. These activities include research and vaccine development projects, activities to create demand for and communicate the value of rotavirus vaccines, and advocacy for the product launches of candidate vaccines. The ADIP builds on the agenda of activities included in the Interim ADIP. The ADIP will include activities considered crucial for accelerated introduction targets that other groups do not currently support. In addition, the ADIP will shape and direct the RAP by acting as coordinator and liaison to other stakeholders. The ADIP was created following discussions with key global stakeholders, the Interim ADIP team, industry, and public-sector constituents. It incorporates the research agenda developed by GAVI's Research and Development Task Force, plus an agenda of activities highlighted by McKinsey & Company. The ADIP for the next three-year window is outlined in detail in Section III.

Throughout the ADIP are scheduled times for reevaluating the plan. During reevaluation, we will look for ways to further compress the timeline and also discuss strategies that should be modified or discontinued. Although there are formal times for reevaluation, it is the intention of the ADIP team to assess progress and modify the RAP and the ADIP on an ongoing basis.

III. Proposed Activities of the ADIP for Rotavirus Vaccines

The ADIP aims to drive an agenda and its resulting activities toward a single goal: accelerating the introduction of rotavirus vaccines in the developing world. The proposed activities defined here will be further developed with the addition of ADIP team members and will be subject to review by the GAVI ADIP Steering Committee with input from the ADIP Technical Review and Advisory Committee (TRAC).

The ADIP for Rotavirus Vaccine builds on the Interim ADIP and the RAP, described in Section II. The ADIP describes in detail the projected, attainable endpoints and milestones of the proposed activities (see A: Rotavirus ADIP Gantt Chart). While the ADIP includes milestones consistent with the requested three-year time frame, it is important to recognize that three years is an interim endpoint in the longer timeline of the RAP towards vaccine introduction (see Attachment B: Rotavirus Action Plan). The activities initiated by the ADIP are anticipated to go beyond the present three-year time frame. When evaluating the ADIP, it is important to place the ADIP in the context of the larger group of activities. The emphasis on activities within the ADIP will evolve with time as the project emphasis changes from demand creation and vaccine development to introduction.

The ADIP is based on the three strategic areas as defined by McKinsey: Establishing Value, Communicating Value, and Delivering Value. During the initial three-year proposal, the natural focus of the ADIP will be on establishing the value of the vaccine among "consumers," communicating the value of these activities, and laying the groundwork for delivering value as the vaccine becomes available. The activities listed below will be modified continually based on new scientific information, results of clinical trials and surveillance studies, and the evolving needs and interests of stakeholders.

A. Establishing Value

"The burden of the disease is established and the benefit of the vaccine is well understood on country level" (ADIP presentation, March 29, 2002, slide 16).

Establishing Value is divided into two key components. The first will gather *disease-specific* information for decision making, especially in the areas of surveillance and cost-effectiveness. This information will help shape advocacy messages to create demand at individual, health care system, and political system levels (demand creation will be discussed below in Section B. "Communicating Value"). The second component focuses on gathering *vaccine-specific* information. In this area we will review vaccine candidates from both multinational and emerging suppliers in the developing world and identify potential areas of support to decrease the timeline to vaccine availability. The focus for the multinational candidates will be on projects that ensure vaccine efficacy and availability for the developing world. With local manufacturers, work will focus on projects that could provide a candidate vaccine for the developing world within a reasonable time frame, with sufficient capacity to address areas of high disease burden and mortality.

Support for Regional and National Disease Burden Estimation and Vaccine Introduction Plans in Priority Areas

In the ADIP's work with the surveillance networks, a guiding tenet will be that each activity should explicitly advance a country or region towards vaccine introduction. Interviews conducted by McKinsey with health ministers and the experience of GAVI and CVP confirm that quality, country-specific data on the impact of rotavirus disease and vaccine will be crucial for any decisions on introduction of new vaccines. For this reason, disease burden and vaccine evaluation studies will be critical during the initial three years of the ADIP. We will evaluate surveillance projects with a regional perspective, so selected countries will provide a good sample for regional disease burden estimates. Not all countries in a region will receive a grant for surveillance; however, technical assistance on routine rotavirus surveillance may be available to countries even if a formal surveillance or disease burden grant is not awarded.

When at least one year of data is available for the surveillance networks, the ADIP team will work with network participants to review the data and share lessons learned within and outside of each network. We will create regional disease estimates based on these reviews and prioritize countries for new and enhanced surveillance projects.

Presently, surveillance networks are operating in Asia and Africa. Preliminary work is complete to establish a network in Latin America, but no funding has been awarded to date. The surveillance network in Asia consists of nine countries. This network has been functioning for over one year and, in April 2002, participated in a symposium to present findings and share lessons learned. The present group of countries will be reevaluated to determine if regional estimates can be accurately made and to select countries for enhanced activities for vaccine introduction projects.

Building on a loose laboratory surveillance network, the African disease surveillance network is in its inception. Two countries, South Africa and Tunisia, have begun surveillance work using the U.S. Centers for Disease Control and Prevention's "Generic Protocol for Rotavirus Disease Burden." Six more countries are planning to start surveillance pending additional funding. The composition of these countries will need to be evaluated to determine the potential for regional estimates. It may be appropriate to evaluate Africa's data needs according to subregions, depending on the variability in data and a country's ability to consider adding an additional antigen to its Expanded Program on Immunization.

The Latin America network has been in the planning stage for almost two years. CVP funding has been set aside to fund the Pan American Health Organization (PAHO) project, but difficulty in building the supervisory framework has slowed the submission of the proposal. When funded, we believe this network could become highly functional in a short period due to the high level of capacity present in the PAHO region.

<u>Core Surveillance Projects</u>

Core Surveillance Project (CSP) grants will be offered to countries with minimal or no quality data on rotavirus epidemiology, disease burden, or strain prevalence. Funds will be made available to establish hospital-based surveillance systems based on CDC/WHO's Generic Protocol. Each country will be expected to develop some national disease burden estimates from the data generated by this

activity and obtain strain prevalence data through capacity building and/or collaboration with regional laboratories. CSP grants will be less than US$50,000 per year of surveillance.

Enhanced Surveillance Projects

Countries in which recently-collected, high-quality data from rotavirus surveillance and research studies are available may apply for Enhanced Surveillance Project grants. Countries will be asked to submit multi-year plans for phased activities that might include surveillance for additional health outcomes (e.g., outpatient, community, or rehydration clinic visits), estimation of rotavirus mortality through surveys or review of national data, surveys for health utilization, studies to estimate costs of rotavirus, cost-benefit studies and policy analyses, baseline intussusception studies, and development of educational and advocacy plans. These grants would also support continued CSP activities, training programs, and field sites for vaccine evaluation projects. Awards will be based on factors such as record of excellence in conducting CSPs, likelihood of introducing vaccine soon after availability, and need for vaccine. Grants would be less than US$200,000 per year.

Vaccine Introduction Projects

Countries with sufficient background data to make decisions to introduce vaccine may apply for Vaccine Introduction Project grants. These grants would support core surveillance and other key activities when appropriate, while additionally supporting vaccine evaluation within the country. The design of the vaccine evaluation will depend on the specific needs of the country and may include immunogenicity and safety trials, pre-licensure efficacy trials, or larger demonstration projects in a defined study population. All this will depend on the remaining data needs of the decision makers and the capability and licensing requirements of the country.

Surveillance activities are guided by two principles:

- Principle 1: Funding for and organization of the surveillance activities will be divided by key regions—Southeast Asia Regional Office (SEARO), Western Pacific Regional Office (WPRO), African Regional Office (AFRO), PAHO, and others. Regional networks will be arranged along WHO regions in consultation with GAVI Regional Working Groups to harmonize the ADIP efforts with GAVI partners' vaccine advocacy and introduction activities. Since we expect that vaccine will be introduced in different regions on different schedules, regional network plans will be created with regional partners, which can advance the goals specific to each region and provide an easy way to manage activities in many countries at the same time. Within each region, countries will be selected that will provide a good sample for creating regional disease burden estimates, while a few countries will serve as regional leaders. These leaders will conduct Enhanced Surveillance Projects as described above, then advance to Vaccine Introduction Projects, serving as champions of rotavirus vaccine introduction in the region. A project officer based in the region would supervise and coordinate each region's activities. The project officer would be supervised by the ADIP Surveillance and Disease Burden Manager and may be based in host organizations that will maximize his or her effectiveness (e.g., PAHO, AFRO).

- Principle 2: The information needs of countries will change over time as they approach vaccine introduction. ADIP support should address these changing needs. This will be done using "graduated" surveillance and introduction grants as described above. This structure both encourages and rewards good work by applicants, and allows us to tailor grants to each country's

specific needs. We would expect that as the ADIP matures, countries would "graduate" from one level to the next, ending in vaccine introduction.

Summary of Surveillance Network Subgoals

During 2003

- Create a map of key countries for surveillance based on need, available disease data, and likelihood of vaccine introduction with regional partners and experts.
- Constitute a TRAC (January 2003).
- Organize a meeting of the TRAC to advise on surveillance strategy and review proposals (February 2003).
- Send award letters to investigators (April 2003).

During 2004-2005

- Conduct regional meetings to coordinate data sharing and advocacy.
- Conduct annual evaluation of study progress and award decisions.
- Evaluate new proposals, as appropriate and make decisions about "graduating" countries to the next grant level.
- Publish scientific manuscripts from the Asian Surveillance Network and the African Surveillance Network.
- Create regional disease burden estimates in SEARO, WPRO, and PAHO.
- Initiate surveillance networks in Africa and Newly Independent States, if appropriate.

Costing of Rotavirus Disease and the Cost-Effectiveness of Vaccination in Representative or Early Introduction Countries

Diarrhea is a syndrome caused by many different pathogens. Even when a vaccine controls rotavirus disease, countries will need to maintain treatment systems based on oral rehydration therapy. The major question facing health ministers in developing countries will be, What is the impact (in terms of lives and costs saved) of rotavirus vaccines? Therefore, we also need to evaluate information regarding costs and the synergy with or replacement for other diarrheal disease treatment interventions. The costs associated with rotavirus diarrhea and the cost-effectiveness of vaccination will be major factors for vaccine acceptance by policy makers. However, few such data exist to facilitate these decisions. The cost-effectiveness tools under development from the Interim ADIP will begin a uniform system for the collection of these data. When developed, these tools can be applied in sites where Enhanced Surveillance Projects are underway, making these data available for decision makers.

Summary of Cost-Effectiveness Subgoals

During 2003

- Finalize work of Interim ADIP and help develop generic methods to determine costs and cost-effectiveness data. These methods will take into account the key advocacy and communication messages needed for a global launch of a rotavirus vaccine.
- Collect data in five countries that are regionally representative or that are projected to introduce vaccines early.

During 2004-2005

- Expand use of economic analysis tools in countries supported by ESP and VIP grants.
- Make tools available on WHO and ADIP websites.

Support for Vaccine Development and Evaluation

The initial rotavirus vaccine was shown to be efficacious and then pulled from the United States market due to safety concerns. There remains a risk that other rotavirus vaccines could elicit the causal relationship with intussusception as well. This risk will have to be considered in the support of any vaccine candidates and in the evaluation of vaccine safety. Because of this history, reliance on only one rotavirus vaccine for the developing world may be a risky approach. Thus, pursuing more than one vaccine development strategy seems prudent. In general, candidate vaccines are manufactured by either multinational vaccine manufacturers in Europe or the United States or emerging suppliers in the developing world.

Support for these candidates is described below. The TRAC will advise the ADIP team concerning decisions for support of vaccine development. All candidates will be evaluated by a minimum set of go/no-go decision points during development. Additional decision points will be defined as appropriate for the specific candidates.

Vaccine Candidate-Specific Go/No-Go Decision Points for Three-Year Window

- Plan for vaccine evaluation of the candidate in developing countries.
- Plan for vaccine introduction in developing countries within acceptable time frame.
- Manufacturing capacity to satisfy developing-country demand.
- Favorable risk-benefit for vaccine introduction in developing countries.
- Demonstrated heterotypic serotype protection (e.g., against G9 strains) from Phase III trials.
- Acceptable price-volume agreement.

Support for Crucial Field Trials of Multinational Company Vaccine Candidates

The ADIP team will work with multinational companies to help address and minimize obstacles to using rotavirus vaccines in developing-country vaccine programs. Awards will be based on the following factors:

- The importance of the trial to the ultimate introduction of vaccine in the developing world.
- The viability of the vaccine candidate for use in developing countries and the timeline to availability.
- The scientific merit of the proposal.
- The experience of the site and investigators.

Contracts will be awarded in accordance with the Window 3 guidelines regarding supporting clinical trials. The request for proposals will be available for competition among all interested manufacturers; the mechanism of funding will be transparent.

In order to better communicate with industry partners and negotiate contracts of mutual benefit, it is necessary to have a better understanding of the cost of production of future vaccine candidates. One additional activity to be initiated by the Interim team for use by the permanent ADIP team will be costing studies. These data have been extremely valuable in other projects similar to the ADIP and

will be valuable in assessing the amount of investment needed for ongoing work with multinational companies to have the best product at the lowest cost for the developing world.

Summary of Multinational Vaccine Development Subgoals

During 2003

- Initiate costing studies for vaccine candidates.
- Work with manufacturers to form proposals that support the mission of the ADIP.
- Meet with TRAC to advise on the proposals (March 2003).
- Initiate contracts with companies (March 2003).
- Define activities in the scope of work.

During 2004- 2005

- Provide technical and project oversight.
- Ensure milestones are met and go/no-go decisions are followed.
- Conduct a semiannual review of progress.
- Milestone: Rotavirus vaccine candidate submitted for licensure in at least two regions.

Request for Proposals From Emerging Suppliers in Developing Countries for New Vaccine Development

The ADIP will encourage the production of quality rotavirus vaccines by emerging suppliers. There are two goals for working with emerging suppliers: the first is focused on the development and availability of rotavirus vaccines (establishing value), and the second is focused on the supply of rotavirus vaccines (delivering value).

It is understood that the risk/benefit ratio of rotavirus vaccination differs between the developing and developed world. There is an assumption in the rotavirus community that a vaccine made in a developing country for developing countries may be able to have a different risk/benefit equation applied to it than a vaccine made by a multinational company. There are currently three vaccine candidates being developed in partnerships with companies in India, China, and Indonesia. PATH currently has four Strategic Programs, MVI, MVP, CVP, and Technology Solutions, that have formed vaccine or technology development partnerships with emerging suppliers, and this approach is already being successfully piloted for rotavirus vaccines as well. A public-private partnership between Bharat BioTech Ltd and partners in India (AIIMS/IISc) and the United States (Stanford/CDC) has been initiated with support from CVP, the Indo-US Vaccine Action Program, and other donors. Similar collaborations have been discussed or already initiated. Additional support for the most promising of these may expedite ultimate introduction of rotavirus vaccines.

In the first six months the ADIP will review these companies' interests in progressing with their candidates and their partners and then assess the capability of the partnerships to develop, test, and license a rotavirus vaccine. If the projects are found to be feasible, the ADIP team will review the candidates to see which should have further investment from the public sector and work with the partners to develop a scope of work, budget, and project milestones that would become part of a funding agreement.

The role of emerging suppliers in supply is linked to, but should be considered separately from, their role in vaccine development. Options for how the supply can be reached are: (1) one manufacturer

(multinational or emerging supplier) makes sufficient doses for the developing world, (2) several different rotavirus vaccines are developed and supplied from different sources, and (3) a vaccine may be developed by one company but manufactured through other suppliers. The number of doses required to immunize children is likely too large for any one manufacturer to supply, so eventually there will need to be several manufacturers of rotavirus vaccine. It will be costly to fund the development effort of several different rotavirus vaccines so practically only one to two of the emerging suppliers' vaccine development efforts can be partially funded from the ADIP. Another possibility is to build in partnerships—either emerging supplier to emerging supplier or multinational supplier to emerging supplier—for technology transfer to achieve supply of a sufficient number of doses. The issues of supply will be more fully addressed during the first year of the ADIP project so that a strategy—that will likely involve emerging suppliers—can be developed. A rigorous demand forecast will also be necessary to understand the phasing that will be necessary for supply.

Summary of Emerging Suppliers Vaccine Development Subgoals

During 2003

- Create a list of candidates presently under development, with their characteristics, for use by the permanent ADIP team.
- Create the framework for interacting with emerging suppliers and a strategy for ranking candidates.
- Meet with TRAC to review and score the proposals (March 2003).
- Initiate contracts with companies (March 2003).
- Provide technical support to initial grant recipients to develop multi-year development and testing strategy.
- Complete final development plan proposals along with ADIP project officer consultation (November 2003).

During 2004-2005

- Review final development grants by TRAC (March 2004).
- Award development grants to one or two applicants by ADIP team (March 2004).
- Provide technical and project oversight.
- Ensure milestones met and go/no-go decisions are followed.
- Conduct semiannual review of progress by technical advisors.
- Milestone: Emerging supplier rotavirus vaccine candidate pilot lot ready for Phase III trials.

Global and Regulatory Vaccine Development

In support of the creation of a successful licensed rotavirus vaccine, several tasks remain at the global and regulatory levels. First, WHO must develop guidelines for rotavirus vaccine production. These guidelines will assist in vaccine production and facilitate vaccine licensing. Supporting the creation of these guidelines will be an important activity of the ADIP and will help us ensure that supported vaccine candidates meet the qualifications for WHO pre-qualification.

We will also share data on demand and introductory plans with the United Nations Children's Fund (UNICEF), as UNICEF can help facilitate and plan vaccine procurement for the developing world.

During 2003

- Finalize WHO guidelines for rotavirus vaccine production (WHO).

During 2004-2005

- Support vaccine candidates made according to WHO guidelines.
- Support candidates submitted for pre-qualification from WHO.

Creation and Use of a Small Grants Mechanism to Fund Crucial Unmet Needs

A Small Grants Fund will create flexibility within the ADIP and help us be responsive to new needs, and fill unforeseen gaps. The activities funded by the Small Grants Fund do not fall clearly under the main ADIP project areas and are often discrete, short-term projects that require minimal financial support. Examples of these activities are supporting key meetings and consultancies, developing methods or protocols, providing laboratory support and training, and transferring technology. Supporting these key activities will require a flexible, easy-to-use funding mechanism. The Small Grants Fund will be established for this purpose and will disburse funds based on the merits and importance of proposals at the discretion of the ADIP Director. These projects may be reviewed by the TRAC if necessary. A limit of US$75,000 would be set, and a project could only be funded for a single year, with reevaluation prior to any refunding.

Summary of Gap Filling Subgoals

During 2003

- Create guidelines to govern use of Small Grants Fund managed by ADIP.

During 2004-2005

- Reevaluate the usefulness and need of Small Grants Window.

B. Communicating Value

"A message that convinces the decision makers to prioritize introduction of vaccine in the country" (ADIP presentation, March 29, 2002, slide 16).

Communication for Decision Makers

There is a paucity of information available to global, regional, and country-level decision makers allowing them to make evidence-based decisions. The goal of the ADIP is to more fully understand the key information needs at the global, regional, and country levels; ensure that the ADIP activities will generate data to address those needs; and then provide the information to the right people at the right time. This approach, while standard in the private sector, has not previously been applied to vaccines for the developing world. Part of this project will be hypothesis testing as assumptions are often made about the types of information needed for decision making. Modeling studies by Mark Miller as part of the Children's Vaccine Initiative suggest that the real factors associated with vaccine uptake in a country do not always coincide with assumptions that come out of the research community. To address this, ADIP team members will require qualitative insight into the existing knowledge, perceptions, and beliefs of key decision makers and the obstacles specific to a country's capacity to introduce a rotavirus vaccine. "Audience Research" is a proven mechanism to collect and interpret these data. The Interim ADIP initiated a survey sample of key officials that will be finished in the first year of the ADIP. This survey will help us refine the direction and define the advocacy and communication strategy. If successful, another similar study might be conducted later to evaluate progress towards demand creation in this group. This activity has been and will be coordinated with the pneumoccocal ADIP managers.

The ADIP team will utilize the World Health Assembly and its Regional Committees to share messages and to obtain a resolution on rotavirus. This mechanism will provide access to all Ministers of Health in the world, thereby accessing the key target audience en masse. This mechanism also will ensure the priority of rotavirus in the global health agenda.

National communication plans will be facilitated and fine-tuned as national governments move forward to decide on rotavirus vaccine introduction. We can augment these plans by creating and sharing advocacy, communication, and training tools that can then be adapted to national needs.

In light of the present timelines, a strategic plan for advocacy and communication will build off of the experience of the Malaria Vaccine Initiative, the Meningitis Vaccine Project, and the Children's Vaccine Program communications teams. This plan will help direct further investments in strategic study questions and will build off of the audience research that is being conducted as an interim activity.

All of the activities contained in the ADIP directly address the needs of key constituents, and in doing this, lead towards the use of a rotavirus vaccine.

Communication for Decision Makers Subgoals

During 2003

- Review proposals and award grant to a company skilled in audience research based on RFP published by Interim ADIP team (December 2002).
- Recruit full-time Advocacy and Communication Manager for Rotavirus ADIP team (February 2003).
- Finalize data collection instrument (February 2003).
- Create initial advocacy and communication strategy.
- Finish interviews and produce report (June 2003).
- Utilize report to reevaluate the ADIP and further define the advocacy and communication plan.
- Milestone: Create an ADIP website to share data and information for decision making.

During 2004-2005

- Approach Regional Committees for including rotavirus on the agenda for consideration by the World Health Assembly.
- Repeat audience research to monitor progress, changing attitudes, and effectiveness of the various ADIP activities towards creating demand.
- Facilitate national communication plans.

Scientific Communication

The science and public health communities working on rotavirus and rotavirus-related issues will be key advocates for a vaccine when it becomes available. It is vital that these groups are up to date on the status of new vaccines and other data that can help them advocate for rotavirus in their countries and regions. The ADIP team will encourage publication of surveillance study data and will communicate the data to the public health care system. An international rotavirus meeting would

serve as an ideal forum to update scientific advances in the field, review progress of vaccines under development and in clinical trials, renew enthusiasm for a vaccine, create effective messages for advocacy, and create new champions for the vaccine. The meeting would also serve as a forum to present the first data from the ADIP-supported surveillance sites and lobby for a Global Rotavirus Vaccination Policy. At that time, we could also solicit further commitment for procuring rotavirus vaccine from GAVI and The Vaccine Fund and pursue potential avenues with other donors. As reliable demand has been identified as a key area impacting industry's commitment to rotavirus vaccine production, these steps could be pivotal in ensuring demand and, therefore, securing industry support for production capacity for the developing world. This commitment and the results of this meeting would be used to refine the demand estimates.

Surveillance networks can provide data to create regional disease estimates as mentioned in Section A. "Establishing Value." These estimates will be presented to the WHO Regional Offices and GAVI Regional Working Groups to foster support for regional vaccination policies. The ADIP team will work with these regional entities to sketch out a regional vaccine introduction plan. The introduction plan will be used to refine the demand estimates. This process would be repeated in each region, bringing the lessons learned from previous regions to assist in the process in subsequent regions.

Summary of Scientific Communication Subgoals

During 2003

- Convene a large, international scientific symposium on rotavirus (spring or fall 2003).
- Utilize the ADIP website to share data and progress.

During 2004-2005

- Present regional rotavirus disease burden estimates to SEARO, WPRO, PAHO, and the associated Regional Working Groups.
- Progressively refine demand estimates as disease burden estimates are improved.
- Milestone: A Global Rotavirus Vaccination Policy.
- Milestone: Regional Rotavirus Vaccination Policy in Asia, South Asia, and Latin America.

Communication for Global Decision Makers and Funders

Special attention should be given to global decision makers and funders who can influence national and regional decision making. These key constituencies can use data from surveillance and cost-effectiveness studies to advocate for rotavirus vaccine introduction. Providing information to these decision makers and funders is an ongoing process that requires international scientific presentations and global advocacy through GAVI, WHO, and other international partners. The success of this work will ultimately impact the sustainability of rotavirus immunization. Because the cost of routine immunization programs increases with time, funding for these programs must also increase, whether by direct national resources or by leveraging international support of various counterparts. Either way, in many countries, donor support for introduction activities and ongoing financing will be essential.

Summary of Communication for Global Decision Makers and Funders Subgoals

During 2003

- Create an advocacy and communication plan to address the communication and data needs of this group.

During 2004-2005
- Evaluate and refine the plan.

Global, Regional, and National Training and Technical Support
As global and regional rotavirus vaccination policies are created, we will need to train a cadre of trainers on rotavirus-specific issues. These trainers would be available for training trainers at the national level. Countries will also need support in creating national introduction plans that include training, cold storage, transportation, waste management, and financial sustainability planning. All of these resources will be available from the global and regional levels to assist countries.

Summary of Training and Technical Support Subgoals
During 2003
No specific activities until vaccine specific data becomes available.

During 2004-2005
- Milestone: Create training-of-trainer materials and modules for adaptation at the national level.
- Provide technical support to countries for vaccine introduction activities.
- Milestone: Conduct training of trainers at global level and in SEARO, WPRO, PAHO (AFRO is anticipated in early 2006).

C. Delivering Value

"Reliable and sustainable supply of the vaccine, and continued prioritization by national authorities" (ADIP presentation, March 29, 2002, slide 16).

Delivering value ensures that vaccine is available to all those in the developing world who need it. The ADIP will continue to improve demand forecasting so that industry can ensure vaccine supply and so that the global community understands the potential level of support required for vaccine introduction. Within the ADIP's three-year time frame there will be little opportunity for additional activities in this area, as candidates will not be available and licensed during that time frame. However, we will set the basis for the sustainable supply of vaccine and prioritization by national authorities. The backbone of diarrheal and rotavirus surveillance will allow for an impact assessment of vaccination and thereby reinforce the decision to vaccinate. This data will be particularly important, as rotavirus is only a single cause of diarrhea. Even with a 100 percent efficacious vaccine and 100 percent coverage, children will continue to have diarrhea and be hospitalized due to dehydration. Without adequate baseline data and ongoing surveillance, the vaccine impact could be lost and, with it, the political support to continue vaccination. This issue also demonstrates how closely the ADIP strategic areas must function to be successful.

Delivering value will be based upon strong working relationships with industry, both multinational and emerging vaccine suppliers. We will make communication between industry and the ADIP team a strong priority and will time activities to ensure that industry expectations and production capacity are in line with public-sector workplans. This dynamic relationship will allow us to maximize the use of resources and streamline vaccine introduction.

Besides setting the groundwork for delivering value, the three-year ADIP should be able to begin rotavirus vaccine demonstration projects. These demonstration projects will be set in key countries within the regions to show the vaccine effectiveness and to reinforce the regional vaccination policy. Demonstration projects will also be used to collect Phase IV safety data.

Develop Improved Demand Forecasts

According to McKinsey's analysis, the single greatest obstacle to expediting testing and supply of new vaccines in developing-country settings is the uncertainty of the demand for new vaccines. Multiple factors play a role in creating demand. An effort to explore these factors and to create reliable, believable demand and introduction forecasts will be a crucial step towards ensuring adequate supply to countries. For the public sector, we will identify the factors responsible for the gap between need and demand and create an action plan to address the key barriers to introduction. A preliminary model for forecasting rotavirus vaccine demand was created by CVP, the Interim ADIP team, and the McKinsey team. This model will be further developed, and work at the global and country level will commence to develop more refined forecasts. It is vitally important that these forecasts be developed not by disease advocates, but by more impartial market-oriented individuals. Ongoing discussions with the interim pneumococcal ADIP team will ensure this work is coordinated, efficient, and consistent between ADIPs. This work will be done in collaboration with the newly formed GAVI Vaccine Provision Project, which will also be working on demand forecasting and with close communication with UNICEF and the GAVI Financing Task Force.

One key piece to predicting demand is the commitment of resources to procure the vaccine. The ADIP team will work with GAVI and The Vaccine Fund to try to establish a commitment to purchase vaccine via The Vaccine Fund. This process will begin early in the new ADIP, but will be an ongoing, iterative collaboration with public-sector and private-sector experts. Additionally, the ADIP team will work closely with the GAVI Financing Task Force (FTF) on the use of existing and the creation of new mechanisms to ensure financing of vaccine purchase and delivery. It is also anticipated that the ADIP work with industry will benefit from the analyses and insights being produced by the FTF.

<u>Global ADIP Go/No-Go Decision Points for Three-Year Window</u>

- Milestone: GAVI commitment to purchase rotavirus vaccine for The Vaccine Fund-eligible countries.
- Explore other financing options with the FTF.

Summary of Demand Forecast Subgoals

<u>Annual</u>

- Develop a more robust model for demand forecasting.
- Revise the initial seven-year demand forecast for The Vaccine Fund-eligible countries.
- Develop and revise forecasts for middle-income and developing countries.
- Identify the main barriers between "need" and "demand" and revise the ADIP workplan to address these barriers accordingly.
- Maintain communication and links with other groups working on forecasting demand through regular meetings (UNICEF, industry, CVP, MVP, MVI, and others).
- Work with GAVI to determine the resource requirement for purchasing rotavirus vaccine.
- Communicate often with industry partners so they can match capacity with demand.

During 2004-2005

- Prepare sites for demonstration projects by beginning Vaccine Introduction Project surveillance funding as described in Section A. "Establishing Value."

D. Summary of Overall Decision Points During Three-Year Window

The proposed ADIP plan is designed to have a set of attainable subgoals within each workplan to monitor progress and provide points for further evaluation. Some of these subgoals are points at which a decision will be made to continue with the plan or to re-evaluate and change the strategy or direction of the plan within that specific area which we have defined as go/no-go points.

If we look specifically at the go/no-go decision points, we see they fall into two categories. At the plan's inception these points are limited and more may be developed over time by the ADIP team and/or the GAVI ADIP Steering Committee. The go/no-go decision points are listed below.

Global ADIP Go/No-Go Decision Points for Three-Year Window

- Milestone: GAVI and The Vaccine Fund make a commitment to purchase rotavirus vaccine for The Vaccine Fund-eligible countries.

Vaccine Candidate-Specific Go/No-Go Decision Points for Three-Year Window

- The manufacturer has a plan for vaccine evaluation of the candidate in developing countries.
- The manufacturer has a plan for vaccine introduction in developing countries within an acceptable time frame.
- There is planned manufacturing capacity to satisfy developing-country demand.
- There is a favorable risk-benefit for vaccine introduction in developing countries.
- Demonstrated heterotypic serotype protection (e.g., against G9 strains) from Phase III trials.
- An acceptable price-volume agreement reached.

Global Go/No-Go Decision Point

The first go/no-go decision point is focused directly on the central issue of the ADIP–reliable demand; a part of that reliable demand is a commitment to purchase rotavirus vaccine for The Vaccine Fund-eligible countries through GAVI and The Vaccine Fund. According to McKinsey's research, unreliable demand is the primary factor influencing multinational vaccine manufacturers in producing vaccine, especially vaccines for the developing world. As the ADIP will focus on trying to further define the demand and increase it, the obvious first place to start is with the Alliance itself. GAVI has shown a commitment to rotavirus vaccine through the creation of the ADIP but this commitment has not yet been defined when it comes to the anticipation of vaccine purchase. When the ADIP team begins to work more with industry to further its commitment to producing a vaccine for use in The Vaccine Fund-eligible countries, the commitment to procure the vaccine by GAVI and The Vaccine Fund must become further defined. This commitment will likely develop over time, as will the level of commitment of industry to move forward or make price-volume agreements (as the characteristics of the vaccines and their production costs become clearer). We feel this is the first appropriate go/no-go decision point, however. If GAVI and The Vaccine Fund are not able/willing to make a commitment to procure the vaccine for The Vaccine Fund eligible-countries, the basic

premise of assuring demand comes into question. That being said, work will also need to be done with GAVI partners and other donors to support rotavirus vaccination through mechanisms independent of The Vaccine Fund. These efforts are further defined in the advocacy and communications portion of the ADIP plan.

The timeline for this decision point is in Q1 2003, but will have to be coordinated appropriately with GAVI and ongoing GAVI meetings. This commitment would be revisited as the vaccine candidates progress and to further leverage commitments on price-volume from industry partners.

Vaccine Specific Go/No-Go Decision Points

The next set of go/no-go decision points are focused on specific vaccine candidates. Each of these points would need to be applied individually to the vaccine candidates considered for support by the ADIP. For example, the first three points are useful in looking at which manufacturers the ADIP would be interested in supporting. The vaccine candidates considered for ADIP support would need to demonstrate a plan for vaccine evaluation in developing countries, a plan for vaccine introduction in developing countries within an acceptable time frame, and manufacturing capacity to satisfy developing-country demand. If these factors could not be met, the decision to work with that candidate would be a "no." This decision would be reached for multinational manufacturers in Q1 2003. With respect to emerging suppliers, the investment would need to be weighed against the morbidity and mortality addressed by the introduction of the candidate in its country of development and the likelihood of licensure outside of that country. This initial data would be anticipated by Q4 2003 for emerging suppliers.

The reasons for these decision points are varied but all focus on creating a reliable vaccine supply for the developing world. Because historically it is known that vaccine immunogenicity and efficacy has varied between the developed and developing world, the ADIP would not be interested in pursuing the support of a vaccine candidate if there is no plan or willingness to evaluate the vaccine candidate in the developing world. Likewise for point two—a plan to introduce the vaccine in a timely manner in the developing world—these two points would be starting points in the go/no-go decisions to work with industry partners. The third point may not be known at the time of initial conversations with industry partners, but should be built into any agreements for support. If this requirement cannot be met, this would be reason to discontinue support for a candidate.

The next two points are characteristics of the vaccine itself that will need to be met to be supported by the ADIP: favorable risk-benefit for vaccine introduction in developing countries and demonstrated heterotypic serotype protection (e.g., against G9 strains) from Phase III trials. These points would be included in the annual workplan and assessed by the ADIP team and discussed with the TRAC as needed. If a vaccine candidate could not meet these characteristics the decision would be a no go. The timeline for these points would be developed in the plan as the relationships and arrangements for support with industry are defined in Q1 2003 of the ADIP. These characteristics may not be known during the initial negotiations with industry but should be built into any agreement as studies in the developing world move from Phase I and II trials to potentially larger investments in Phase III trials or other production support. The timeline for these decision points will have to be set by the individual candidates' development timelines.

The final point directly identified by McKinsey was the need for an acceptable price-volume agreement. This likely will also be a staged agreement. As the vaccine candidate passes milestones or the above go/no-go points and additional investments are considered by the ADIP, industry will also need to make commitments on vaccine pricing and capacity. The exact nature of these agreements will need to be defined individually with each manufacturer and each candidate. Different options may be available for different candidates (i.e., different fill finish options or emerging supplier partnering) that would impact both price and volume. The price-volume agreement would need to be carefully constructed and followed by the ADIP Director with assistance from the business development team at PATH and supported by the ADIP Steering Committee. Final terms of the price-volume agreements will need endorsement from the GAVI ADIP Steering Committee as implications of GAVI commitment for procurement would be required. If an acceptable price-volume agreement cannot be reached, this would be a no go for that candidate.

IV. Proposed ADIP Organizational Structure and Personnel

Historically, many partners have guided efforts to develop rotavirus vaccines and promote a global agenda for their introduction. Each has brought different visions and strength to the activity. The goal of this ADIP is to further develop these partnerships by soliciting the strong participation of the other major global players, in particular WHO and CDC. This collaboration provides synergy and strength to pursue a common agenda for rotavirus vaccine development and introduction while recognizing that, given the complexity of the task, no single group or organization could achieve this goal alone. At the same time, the need for coordinated leadership will be essential if progress is to be made rapidly and efficiently.

A. ADIP Host Organization: Program for Appropriate Technology in Health (PATH)

PATH, a nonprofit 501(c)3 organization, is a U.S.-based international, nongovernmental organization dedicated to improving the health of people in developing countries through innovations in technologies, programs, and policies. Founded in 1977, PATH identifies, develops, and applies appropriate and innovative solutions to public health problems, especially in low-resource settings.

Most of PATH's innovative projects are implemented through collaboration with local organizations, governments, development agencies, and commercial firms. PATH operates out of 21 sites: 9 in South and East Asia, 2 in South Asia, 4 in Africa, 1 in Europe (Ferney-Voltaire), 1 in the former Soviet Union (Ukraine), 1 in Latin America (Nicaragua), and 3 in the United States (Seattle, Washington, D.C., and Rockville, Maryland). PATH's headquarters includes the Office of the President and the Administration, Finance, and Human Resources Units, and is located in Seattle, Washington. For further information, see Attachment C, PATH's Annual Report.

With 24 years of experience in technology development, advancement, transfer, and introduction, PATH is well qualified to host the GAVI ADIP. Through CVP, we have played a pivotal role in the formation of GAVI and in the creation of The Vaccine Fund. Because of this, we have a deep appreciation for the challenges and strengths of the partnership and the development of the ADIP concept. CVP's rotavirus activities are in alignment with and in support of the GAVI rotavirus agenda, which is the basis for the present ADIP. CVP has been a key player in the development of

the ADIP plan through a strong collaboration with CDC and other partners. PATH is an organization with extensive experience in managing and supporting self-directed teams. The organization is structured around programmatic teams linked with supporting administrative and information networks and fiduciary oversight. For example, MVI and MVP are fairly autonomous teams with different external partners and advisory structures, but each has a cohesive program that takes advantage of the other's experiences.

B. ADIP Primary Strategic Partners

The goal of this ADIP is to develop a plan that will continue to respect and expand the roles of key partners, with strong leadership and coordination provided through the core ADIP team. As part of this plan the ADIP structure has included WHO, CDC, and CVP as Primary Strategic Partners to increase the effectiveness of these powerful groups working together toward this common goal.

World Health Organization (WHO)

WHO, through the Diarrheal Disease Control Programme and then the Global Programme on Vaccines, has made rotavirus vaccine development a high priority. For several years WHO has convened a global forum to bring together interested parties to discuss the direction and development of agendas for rotavirus vaccine. These activities are conducted in four separate areas.

- The Steering Committee on Diarrheal Disease Vaccines has maintained a small grants program that supports studies of disease burden in developing countries. The Committee also set up and supported WHO Laboratory Reference Centers for Rotavirus, and supported vaccine trials with past and present vaccines to assess their immunogenicity and efficacy in countries not targeted by the vaccine manufacturers. When the problem of intussusception was first recognized in the United States, WHO was quick to fund studies to examine the epidemiology of intussusception in developing countries and assess whether the risk-benefit equation for developing countries might nonetheless still favor the use of the original vaccine.

- The Biological Activity Group develops guidelines for the production of new vaccines, provides validated cell substrates for vaccine manufacture, and maintains ties to National Reference Laboratories to help assess vaccine quality. WHO helps national regulatory agencies develop methods to screen and approve new vaccines; train staff; and meet higher, independent standards.

- WHO assists in the approval of new biological products and facilities to ensure that the vaccines produced are safe and efficacious. WHO pre-qualification is required by UNICEF and other organizations for the purchase of vaccines for global programs for childhood immunizations.

- As rotavirus vaccines come closer to introduction, WHO's role will increase as WHO maintains a global network of regional and country offices with staff specifically assigned to the Expanded Program on Immunization (EPI) and new vaccines. For advocacy of new vaccines globally, this network can provide an important base for educational, advocacy, and implementation activities and support to countries.

WHO's role as a Primary Strategic Partner of the ADIP would involve multiple activities (see Attachment D: WHO Letter of Common Interest). WHO may also participate in the GAVI ADIP

Steering Committee and the TRAC as a member of GAVI and the GAVI Board. WHO activities towards the common goals of the ADIP would potentially include, but not be limited to:

- Support toward surveillance networks in Africa.
- Work with Vaccine and Biologicals to facilitate National Regulatory Authority assessment and enhancement in projected early introduction countries and countries where vaccine development will occur.
- Work with the EPI to conduct training and advocacy activities regionally and within countries.
- Coordinate activities of the Initiative for Vaccine Research regarding "upstream" activities to ensure added value and efficiency.
- Develop a cost estimation tool and pilot test it in selected countries.

Centers for Disease Control and Prevention (CDC)

CDC has established a global program for rotavirus research that integrates both epidemiologic and laboratory activities. These activities began 17 years ago with efforts to assess the disease burden of rotavirus in the United States and develop reference laboratory methods to detect and characterize rotavirus strains. At the same time, the group has maintained a more global perspective, recognizing that the real target for future rotavirus vaccines would be in the developing world. Consequently, the Generic Protocol for Sentinel Hospital Surveillance, developed by CDC and now published by WHO, is being used in more than 20 countries worldwide. Laboratories around the world use basic methods for rotavirus strain characterization developed at CDC. CDC serves as a WHO/PAHO Reference Laboratory for Rotavirus and has been a key technical advisor to WHO, CVP, GAVI, the World Bank, and UNICEF on rotavirus. CDC has also provided consultation to all of the major vaccine manufacturers and many of the national producers on the rotavirus epidemiology and disease burden.

A key activity of CDC has been training. CDC has hosted visiting epidemiologists and laboratory scientists and supported surveillance activities in more than 30 countries. Through the Epidemic Intelligence Service, many epidemiologists have been trained at CDC who are knowledgeable and have experience working with rotavirus. An active post-doctoral program has been ongoing for 16 years and the laboratory provides research opportunities for students seeking masters and doctoral degrees. More than 250 publications from CDC on rotavirus have added to the scientific basis for understanding issues related to the disease burden of rotavirus, the evolution and diversity of strains, the efficacy of new vaccines, and prospects for disease control through the use of vaccines. Finally, CDC has worked as an active partner with WHO, CVP, GAVI, and others to promote a global agenda for rotavirus and to provide technical expertise to field activities.

CDC is a key partner in many ongoing international rotavirus activities, including surveillance networks for rotavirus in India and Asia and a program in Latin America with PAHO that is under development. CDC has supported or conducted field trials with different rotavirus vaccines in the United States, Sweden, Pakistan, Bangladesh, India, and Venezuela. The laboratory at CDC has provided reference services and training to many overseas groups working with rotavirus and has been involved in issues of vaccine development. CDC maintains a Good Laboratory Practices facility to prepare seed viruses for vaccine research and for training laboratorians from developing countries in laboratory methods for vaccine production.

CDC will function as a key Primary Strategic Partner of the ADIP (see Attachment E: CDC Letter of Common Interest). This could involve a seat on the Steering Committee and the TRAC. CDC will work very closely with the ADIP team, with two full-time personnel assigned to work on the ADIP. One employee will function as a member of the ADIP team (Figure 1) and a second would remain at CDC as a liaison with CDC/ADIP activities, which would include but not be limited to:

- Management and creation of surveillance networks.
- Technical support to studies of enhanced surveillance.
- Introduction activities as delineated in the ADIP.
- Advocacy support through presentations at scientific and public health meetings.

In addition, the Scientific Director would be employed by CDC until August 2003 and may be located in Atlanta for the duration of the project.

Children's Vaccine Program

Rotavirus vaccine has always been a priority vaccine for PATH's Children's Vaccine Program. We have worked for the past four years to establish the burden of disease by expanding disease surveillance to areas of the world where this information was lacking. We have also supported specific activities to accelerate the development and introduction of new rotavirus vaccines and created a rotavirus expert group, led by Dr. Roger Glass, through our collaboration with CDC. This led to the development of a rotavirus strategic plan that supports the global rotavirus agenda and through which CVP has financially supported extensive surveillance and vaccine development activities. There is significant overlap between the global agenda, CVP's rotavirus activities, and the Interim ADIP strategic plan.

With the advent of the intussusception problem and the withdrawal of Rotashield from the market, CVP supported a rotavirus vaccine consensus conference at WHO that led to the recommendation to pursue the development of alternate rotavirus vaccine candidates. In response, we reformulated the Vaccine Action Plan of the US-India Bilateral Science Program into a newly formulated business development plan to accelerate the production and introduction of an Indian rotavirus vaccine. Two vaccine candidates are being advanced through a collaborative partnership between CVP; CDC; the National Institutes of Health (NIH); Stanford University; the All India Institute of Medical Sciences; the Indian Institute of Science; and a private Indian vaccine manufacturer, Bharat Biotech. This project aims to produce a vaccine that would be developed and produced in the developing world, for the developing world. This project is currently supported by CVP at the level of US$6.5 million, with an expectation of licensure of a vaccine in India by the end of 2006. This project would be closely aligned with ADIP activities.

In addition to its work in rotavirus vaccine development in India, CVP is actively participating in a creative partnership with the public sector and GlaxoSmithKline, called the Rotavirus Action Program for Immunization and Development (RAPID). In this partnership, CVP has been able to provide flexible funding to program areas that cannot be met by other partners, including arranging travel and working directly with industry. RAPID has been successful in funding Phase I and II trials in the developing world in Asia (Bangladesh) and Africa (South Africa). PATH business development and commercialization staff drafted the Memorandum of Understanding for the RAPID partnership and negotiated it on behalf of several public-sector institutions.

Through the ADIP process we will consolidate and expand these partnerships to ensure that several vaccines will meet the objective of widespread vaccine availability for the developing world.

In establishing value through data for advocacy, CVP has been working with partners to create surveillance networks in the developing world. The Asia surveillance network, in partnership with CDC, has projects in nine countries working to establish data for decision making and advocacy. The support CVP provided to four countries leveraged funding for the additional countries that fall outside of CVP's focus on The Vaccine Fund-eligible countries. This network is the prototype for networks in Africa and Latin America. The network in Africa, through the Medical University of Southern Africa (MEDUNSA) and Dr. Duncan Steele, was just funded for two countries, with plans to expand to an additional six countries in the next few years if co-funding is found. The Latin America network, in partnership with CDC and PAHO, will work with six to eight countries that will be early introducers of vaccine and historically have been trendsetters in the region. Through the ADIP process, these networks can be expanded and transitioned into programs to monitor vaccine trials, provide the framework for vaccine introduction, and monitor vaccination program effectiveness.

CVP has selected several The Vaccine Fund-eligible countries where we provide intensified support to help achieve GAVI coverage objectives by the year 2005. These "model programs" involve extensive collaborations with the respective ministries of health, EPI programs, and other partners on the ground. CVP would expect to help these countries introduce and monitor new rotavirus vaccines as part of our on-the-ground team efforts.

It is well acknowledged that the US$30 million available from The Vaccine Fund to the ADIP is not nearly sufficient to fund the comprehensive set of activities required to make rotavirus vaccine available to all of the world's children. CVP's activities, which will continue as part of the overall RAP, will substantially complement the activities of the ADIP. Appropriate integration of ADIP and CVP activities within the PATH administrative structure will provide for seamless coordination and improved synergism. Coordination of activities would be further enhanced by the CVP-funded country coordination manager on the ADIP team, and by ongoing CVP technical and administrative assistance to the ADIP team.

C. The Core ADIP Team

Organizational Structure: Identification/Purpose of Core Team Positions

The full ADIP team has been designed to be a compact team with experience and the necessary skills to successfully refine and carry out the ADIP plan. As detailed in the ADIP documentation provided by GAVI, the ADIP team would focus on: (1) establishing value through surveillance, cost effectiveness, and appropriate clinical trials through clinical program development, demand estimation, and critical analysis; (2) communicating value through education, meetings, and lobbying and refining demand forecasts through communications and advocacy; and (3) delivering value through ensuring vaccine supply, funding, and delivery systems by working with suppliers, countries, and the international community. The skill sets required to successfully carry out these tasks would include epidemiology; statistics and knowledge of clinical trials; communications and advocacy; business development and commercialization; and product launch activities including public health planning, training, and immunization introduction.

The team would be constructed to expand and develop the partnerships and collaborations already existing within the rotavirus community to enhance the skills and human resources of the ADIP team. The structure of the team may need to change over time as activities progress from creating value to delivering value. The initial team will need to incorporate a business development perspective and be more heavily weighted in establishing and communicating value, with a firm plan to move toward delivering value in the longer term.

PATH has a demonstrated ability to recruit and retain senior managers from industry and to successfully manage the creative tension between the technical, public health, and business perspectives. This is perhaps the greatest experience PATH can offer, as it represents a paradigm shift for many in the vaccine community who will work with the ADIP. Having a culture where no single perspective carries more weight than another leads to a balanced approach that is both rational and practical. Proposing a director who is from industry and brings a skill set of product development and launch will ensure that the rotavirus ADIP will balance the more research-oriented perspectives.

Team members will be employed by PATH or seconded to work on the ADIP team by CDC or other collaborating partners. The ADIP Steering Committee will be involved in the selection process and will have input on team selections not already identified in the proposal.

Technical Expertise

The proposed Director of the ADIP team is John Wecker, Ph.D (see Attachment F: Dr. Wecker's Curriculum Vitae and Attachment G: Dr. Wecker's Letter of Commitment). Dr. Wecker has over 16 years of experience in the research-based pharmaceutical industry, 14 of which have been with Boehringer Ingelheim. For the first seven years at Boehringer Ingelheim, he was involved in the design and execution of clinical development programs for new therapeutic drug candidates. Following that experience, he held the position of International Project Leader responsible for leading interdisciplinary product development teams involved in the development of therapeutic drug candidates for the treatment of a wide variety of medical conditions. In his most recent experience, he has been responsible for Boehringer Ingelheim's HIV-related activities in the developing world. Dr Wecker's skills that are of greatest value to the Rotavirus ADIP are addressed in more detail below.

Establishing Product Value

The primary objective of the drug development process is to establish the value of a new drug product. During development, data is successively collected that demonstrates an essential set of characteristics (e.g., efficacy, safety, and convenience) intrinsic to the product. Collectively, these characteristics can be referred to as the Target Product Profile (TPP). Value is generated when these characteristics can be matched to the needs of a customer.

From the time that a new drug candidate enters clinical testing, the drug development process at Boehringer Ingelheim is conducted under the responsibility of a Core Project Team. A Core Project Team consists of a single representative from each of five functional disciplines (Research, Medicine, Drug Regulatory Affairs, Marketing, and Manufacturing) and is led by an International

Project Leader. The primary responsibility of the Core Project Team is to identify, demonstrate and communicate the value of a new drug candidate.

Relevant go/no-go criteria are established on the basis of the TPP. Data collected in successive stages of development can be assessed against these criteria as a basis for deciding whether or not to proceed with the next stage of development. If the assessment is positive, corresponding commitment of financial and human resources can be committed.

The characteristics identified in the TPP are also used as a basis for defining the development objectives for each of the disciplines represented on the Core Project Team. Each representative on the Project Team proposes a successive program of experiments designed to evaluate the likelihood of achieving the strategic objective. An overall product development plan is then created based on the integration of the individual programs.

The International Project Leader is responsible for ensuring that (1) a desirable (i.e., value-generating) TPP for a product is established; (2) the product development plan is appropriately integrated to achieve the TPP in a timely fashion; and (3) the overall development process, including go/no-go decision-making process, remains focused on the goal of achieving the TPP. The Project Leader also serves as the primary interface between the development process and the senior management of the company.

One of the challenges of the drug development process is to create value for a variety of "customers". Key customers can include the patients, key opinion leaders, prescribing physicians, regulatory authorities, and payers. Each customer evaluates the characteristics of the product according to their own individual needs and, therefore, data must be generated during development that demonstrates the value for each of the customers. Failure to create the necessary value for any one customer can jeopardize the ultimate success of the entire development process. Oftentimes during the development process, decisions must be made regarding when to collect data in support of value generation, balancing the need to establish value against the overall probability that a drug candidate will be successfully developed.

For more than five years, Dr. Wecker was the International Project Team Leader for several Core Project Teams responsible for the development of drug candidates for a variety of therapeutic areas. One of these products, an antiretroviral known as Viramune® (nevirapine), was successfully developed and introduced. Since its initial approval in 1996, Viramune has been registered and introduced in more than 100 countries worldwide and has been established as a key therapy in the chronic management of HIV infection, as well as for the reduction of the risk of maternal-fetal transmission of HIV during labor and delivery in the developing world. Clearly, this product has value for the relevant stakeholders in the treatment of HIV infection.

Prior to his responsibility as International Project Team Leader, Dr. Wecker participated as the Medical Representative on a variety of Core Project Teams, including the Project Team responsible for the early clinical development of Viramune. This experience provided him with an in-depth understanding of the clinical development process, including the generation of value for the medical community.

Developing World Experience
In response to the HIV/AIDS pandemic, Boehringer Ingelheim has committed itself to taking steps to significantly increase access to Viramune in the developing world. The delivery of this drug is very similar to vaccinations and is focused on the same population as immunization, infants and mothers. For the past two years, Dr. Wecker has been responsible for developing, implementing, and communicating the company's efforts to fulfill that commitment. The company has defined three major platforms to meet the objective of increasing accessibility, including the practice of preferential pricing for Viramune, donating Viramune specifically for use in the prevention of maternal-fetal transmission, and offering voluntary licenses for the local manufacture and sale of generic nevirapine in select countries where the company has patent rights.

Dr. Wecker has traveled extensively through much of the developing world, meeting with representatives from developing country governments, NGOs, and physicians with the objectives of raising awareness of Boehringer Ingelheim's various programs and collecting feedback regarding the needs of these stakeholders. In addition, Dr. Wecker has been the primary point of contact with the UN system.

Dr. Wecker has also been involved in lobbying efforts with developed country governments with the objective of increasing awareness regarding the worldwide HIV/AIDS pandemic and the response of the research-based pharmaceutical industry. The objective of these efforts has been to influence policy positions in the areas of intellectual property rights and financial commitment.

Finally, Dr. Wecker has been responsible for the internal and external communication of Boehringer Ingelheim‘s HIV-related activities and programs in the developing world.

Summary of Dr. Wecker's Experience
Dr. Wecker has years of demonstrated experience in the drug development process, including the successful development, registration, and launch of a drug which is an integral part of today's therapy for HIV infection. Most recently, Dr. Wecker has been actively involved in the efforts and worldwide debate associated with increasing access to medicines in the developing world. Finally, Dr. Wecker has a demonstrated ability in successfully leading interdisciplinary project teams responsible for identifying, generating, and communicating value of drug products. Taken together, PATH believes that Dr. Wecker's experiences and demonstrated capabilities makes him a strong candidate for the Director of the Rotavirus ADIP process.

Dr. Wecker's experience and skills are considered complementary to the other proposed members of the ADIP team, specifically in the interaction with the industry partners in order to effectively decrease the timeline for vaccine development and introduction.

To complement Dr. Wecker's leadership and business development expertise, Roger Glass, M.D., Ph.D., is the proposed Scientific Director of the ADIP (see Attachment H: Dr. Glass' Curriculum Vitae and Attachment I: Dr. Glass' Letter of Commitment). Dr. Glass has been the "voice" of rotavirus for many years. It is his enthusiasm and initiative that has brought the rotavirus community together with GAVI and helped create the GAVI rotavirus agenda and the CVP rotavirus program accordingly. Dr. Glass is committed to working to make a rotavirus vaccine available to the developing world. As the Scientific Director, Dr. Glass will provide strategic and technical

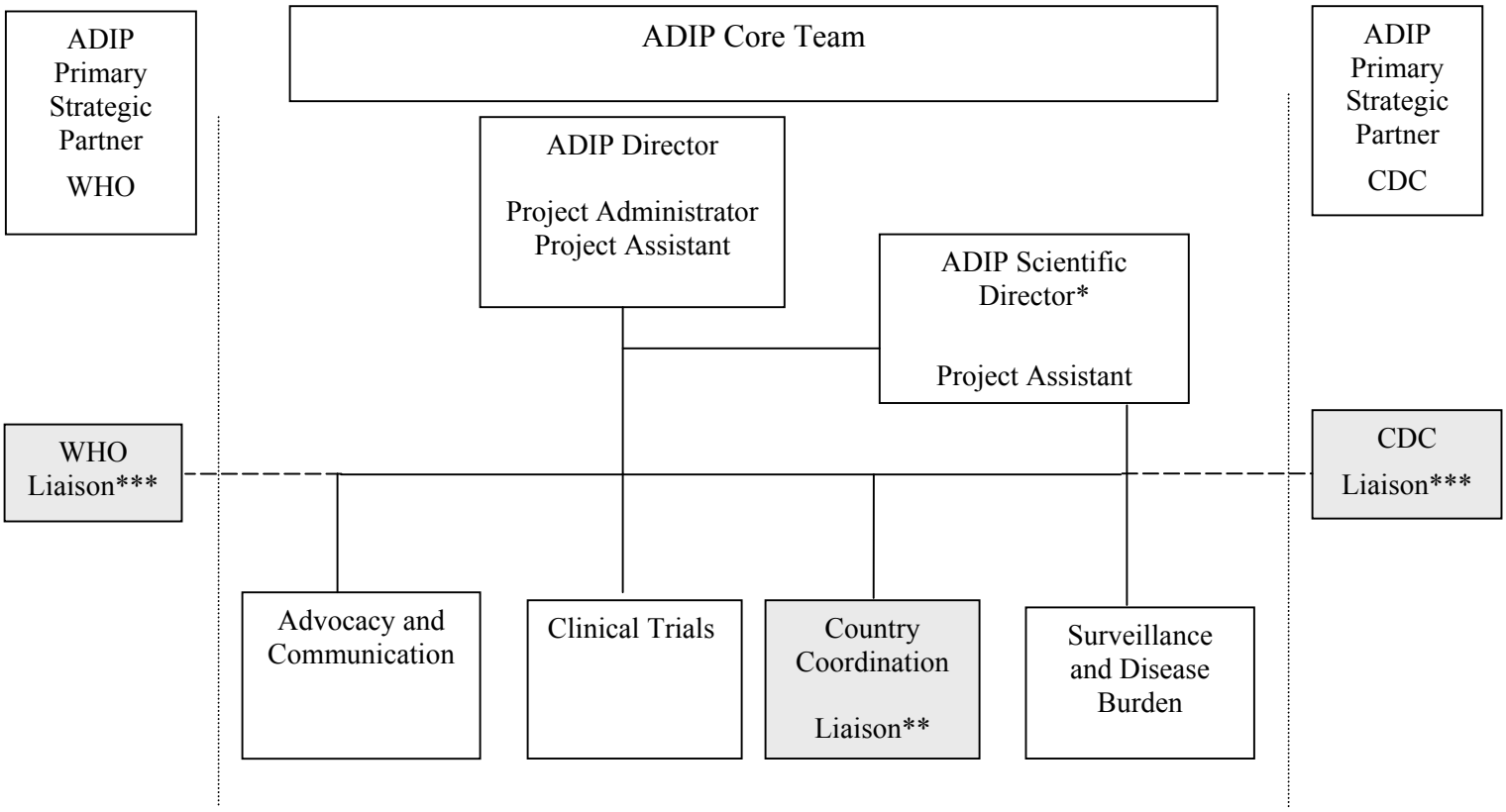
leadership that will effectively bring together the rotavirus community to accomplish the goals of the ADIP. Dr. Glass brings expertise in laboratory diagnosis, epidemiology, and surveillance of rotavirus infection. He is also an expert in rotavirus vaccine research and development. He has led the CDC team that has contributed to much of the current global information on rotavirus disease burden and strain characterization. This team has also trained many of the current rotavirus researchers in the developing world. Dr. Glass is a leading global expert in his field and works exceedingly well with members of the rotavirus community in both the public and private sectors.

As it is the full intention of PATH that the activities of the ADIP should be started without delay, Julie Jacobson, M.D., will take the role of Acting Director until Dr Wecker joins PATH (see Attachment J: Dr. Jacobson's Curriculum Vitae). As initial activities will be started by the Interim ADIP team, this arrangement will allow those activities to continue without a gap in momentum. Dr. Jacobson has been the lead on writing the ADIP proposal in close association with the Interim ADIP team at CDC, WHO, and other partners active in the rotavirus field. Dr Jacobson is highly respected by the international rotavirus community and has been active in working with the rotavirus projects within CVP through her work with CDC, MEDUNSA, the RAPID group, GAVI, and negotiations with PAHO. Her role as the Acting Director would allow the work begun by the Interim ADIP team to continue in transition to the permanent ADIP team. It would be the intention of the Acting Director to work closely with the Scientific Director and the Director as time permits during his relocation time and facilitate his introduction to the rotavirus community and his transition to PATH. Should any unanticipated problems delay or prevent the Director's relocation, Dr. Jacobson would continue as Acting Director until a resolution was reached in consultation with the GAVI Steering Committee.

Team Structure

The primary technical team funded by the ADIP will consist of five people: (1) Director, (2) Scientific Director, (3) Clinical Trials Manager, (4) Advocacy and Communication Manager, and (5) Surveillance and Disease Burden Manager. Three additional team members will be funded through the Strategic Partners. One, working as the Country Coordination Manager, will function as a core team member but be funded through CVP and provide liaison with ongoing CVP activities; a second will be the liaison with CDC, funded by CDC; and the third will be the liaison with WHO, funded through WHO. The team will liaise with the three Primary Strategic Partners through identified liaison positions within WHO, CDC, and CVP. The ADIP Director will provide the overall programmatic oversight and be ultimately responsible for synthesizing data and delivering a unified message to the GAVI Board. The Scientific Director will have primary responsibility for the scientific content of the ADIP and will provide technical input for all team members. The Surveillance and Disease Burden Manager and the Strategic CDC Liaison would be directly supervised by the Scientific Director, who will remain based at CDC in Atlanta, to further strengthen our partnership with CDC. For further details on job descriptions see Attachment K. To facilitate communication amongst team members the team would conduct a weekly team meeting with the use of videoconferencing and/or teleconferencing. This meeting would provide a forum to review the week's events, update team members on issues, and obtain input on project development from the Director and Scientific Director. This is the same process used within CVP to bring the CVP offices together in Senegal, France, Mekong, and the United States. Traveling team members call in depending on their availability. Ongoing communication would be maintained through telephone and email as well as frequent visits between Atlanta and Seattle.

Figure 1: Team Structure



Shaded areas are funded by partner organizations and not by ADIP funding.
* The Scientific Director will be a direct report to the Director but will continue to be based at CDC in Atlanta. Through employment arrangements to be negotiated by CDC and PATH, he will be a full time employee of the ADIP and released from all responsibilities within CDC. Please see Attachments E and I. He will supervise the Surveillance and Disease Burden Specialist and work with the CDC Liaison.
** The Country Coordination Manager will be a position funded by PATH's Children's Vaccine Program and will fill the role of Acting Director until the Director joins PATH to continue the programmatic momentum during the transition.
*** Staff will be liaisons with the ADIP team but will remain as employees funded by their home institution.

Multi-Disciplinary Team Approach
One of the most significant ways that PATH achieves efficiencies and maximizes the use of donor support is by organizing the work internally around multiple interdisciplinary teams. In addition to five core team members dedicated to the ADIP, other PATH staff can contribute to particular activities. This way, the ADIP does not have to support the entire costs of extra staff members, rather their costs are spread across projects. This would include epidemiology, business development and intellectual property, procurement, health economics, advocacy and communications, administrative and financial management, travel support, and computer graphics.

List of Potential Candidates for Other Core Team Positions
- Surveillance/Disease Burden Manager: Dr. Joe Bresee (see Attachment L: Dr. Bresee's Curriculum Vitae)
- Country Coordination Manager: Dr. Julie Jacobson
- Advocacy, Communications, and Product Launch Manager: TBD
- Clinical Trials Manager: TBD

Salary Structure
Salaries for PATH employees are governed by the salary structure outlined in Attachment M. PATH's compensation system consists of two job families: Program Resources, which includes administrative support and mid-level and senior project administration positions and Program Implementation, which includes programmatic support, mid-level program professionals, and senior project and program officers and directors. Each of these job families consists of six grades with ranges for each grade. These ranges incorporate all positions in that grade, exist for each job family, and are broad enough to allow salary growth for at least a three-year period. Each grade is divided into three bands—entry, experienced, and advanced.

With the exception of support positions, most staff hired for this project will likely be placed in the experienced band, which defines a salary subrange appropriate for individuals who have demonstrated the necessary proficiency to perform the standards of their respective jobs and for individuals who have gained or bring extraordinary qualifications necessary to the project. In determining salaries, PATH takes into consideration the individual's salary history, compensation for comparable positions in the labor market, and the salaries of current PATH employees in similar positions.

PATH has negotiated and agreed upon salary and benefits packages with both the proposed Director and Scientific Director that are within the established salary bands, and these figures are reflected in the budget. Individual salaries are not shown to protect confidentiality under prevailing employment law.

D. The GAVI ADIP Steering Committee

Proposed Core Composition
- GAVI Board Member: Dr. Rick Klausner, Bill & Melinda Gates Foundation, Executive Director of Global Health.
- GAVI Board Member: Dr. Chris Lovelace, World Bank, Director Health, Nutrition, and Population, Human Development Network.
- PATH: Dr. Christopher Elias, President.

As described in the RFP, the Steering Committee would include a representative of the host organization. Since within PATH's structure the ADIP director will report directly to PATH's president, we have proposed Dr. Christopher Elias as a member of the Steering Committee. Final composition of the Steering Committee will be determined in consultation with the GAVI Board.

Terms of Reference

As per the RFP, the proposed GAVI ADIP Steering Committee will be composed of GAVI board members and the ADIP host agency (PATH). Additional members could include key donors such as The Vaccine Fund, United States Agency for International Development (USAID), or representatives of the Primary Strategic Partners. The Steering Committee will meet at least annually to approve the annual ADIP budget and workplan, provide key strategic direction through progress toward go/no-go decision points, and provide coordination with their home institutions.

Meetings and Other Communications

The annual Steering Committee meeting would be scheduled during the last quarter of the calendar year, to coincide with the PATH annual budgeting and workplan development process. However, the first Steering Committee meeting would occur in Q1 2003 to approve the initial ADIP workplan and budget. The Steering Committee also would approve any significant changes to the workplan and budget during the year, as necessary. The Steering Committee also would be convened if any unforeseen significant changes in the ADIP annual workplan become necessary during the workplan year. These meetings will be structured to the best ability of the team with regard to the Steering Committee's schedule and responsibilities in their home institutions.

How Interactions With the GAVI ADIP Steering Committee Would Be Structured

Interactions with the GAVI Steering Committee will be on a formal basis through the annual meeting and any emergency meetings that are unforeseen but may become necessary during the duration of the project. Formal communications will be through presentations, the annual workplan, and discussions. Informal communications will be primarily with the ADIP Director and/or Scientific Director for strategic input and direction via email, videoconference, and telephone.

The ADIP Team will report both directly to PATH and to the GAVI Steering Committee. The Steering Committee will approve the annual budget and workplan and will approve any significant changes to the workplan during the year. Day-to-day management and programmatic oversight for the ADIP team will fall within the purview of PATH's current management structure and performance evaluation system. PATH presently works with several quasi-independent teams. The best example of this type of arrangement is the Meningitis Vaccine Project (MVP), which is a partnership between WHO and PATH supported by the Bill & Melinda Gates Foundation. In MVP, the project director reports directly to the president of PATH, but is also responsible to a Project Management Committee composed of four members (two from PATH and two from WHO). Similar to the structure proposed here, the MVP Project Management Committee reviews and approves the annual workplan and budget. In the case of the MVP, the Project Management Committee also served as a decision making body for the recruitment of the director and the approval of other staff positions. PATH also has extensive experience with additional external sources of programmatic accountability through the prior experience with the International Task Force on Hepatitis B Immunization.

Issues and Timing of Go/No-Go Decisions by the GAVI Board During the Three-Year Period of the Rotavirus ADIP

It is envisaged that the ADIP Team's main interaction with the GAVI Board will be via the GAVI ADIP Steering Committee whose membership will include several GAVI Board members. Since the ADIP is a new concept, it is not yet clear to PATH what level of involvement the GAVI Board and GAVI ADIP Steering Committee will desire to have in the decision making of the ADIP team. If we are successful with our proposal, we plan to meet with the GAVI ADIP Steering Committee promptly (January 2003) to discuss expectations around decision making and to decide on clear processes for consultation.

The ADIP team would have annual meetings scheduled with the GAVI ADIP Steering Committee to review the annual workplan which would include several go/no-go decision points. The ADIP team would be empowered, after approval, to move forward with the workplan as outlined. At the first meeting of the GAVI ADIP Steering Committee in January 2003 we would also jointly decide on decisions that required interim consultation between the ADIP Team and the Steering Committee. Unless otherwise specified, at the point that a go/no-go decision point is reached, the ADIP team would inform the Steering Committee if this resulted in a significant change in the annual workplan. A further overview and detailed description of the go/no-go decision points listed in the proposal is given in Attachment A.

Communication directly with the Board can be made as requested, but clearly the GAVI ADIP Steering Committee approval will be needed at several key decision points including:

1. When data is sufficient, review available data and consider a recommendation that The Vaccine Fund support the purchase of rotavirus vaccines for Fund-eligible countries and decide upon GAVI's policy for use of rotavirus vaccines. This would first be addressed in Q1 2003 with subsequent updates on data occurring annually (or when major milestones are achieved) that may influence or further define GAVI's position.
2. Review and approve the key terms of agreements with vaccine manufacturers, including price-volume agreements prior to the final negotiation of agreements, anticipated by end of year 1.
3. Decide if there will be sufficient "return on investment" for GAVI to continue to invest in rotavirus vaccines beyond the initial three-year ADIP period (end of year 2). In order to continue the work with industry, assurances of investments will need to be in place by this time.

The timetable for meeting with the Steering Committee is given below. These dates are included in the Gantt chart included in our proposal.

January 2003 or promptly after approval:

- Meeting to jointly define expectations and plans for consultations between the ADIP Team and the GAVI Steering Committee, discuss transition from the Interim ADIP Team to the ADIP Team, clarify decision-making roles and responsibilities, and agree on a timeline for developing the first year ADIP workplan.

March-April, 2003:

- Videoconference to review and formally approve the first year ADIP workplan.

October 2003 :
- Meeting to review progress and discuss and approve the second year ADIP workplan.

October 2004:
- Meeting to review progress and discuss and approve the third year ADIP workplan.

October 2005:
- Meeting to review progress and discuss future workplans for the Rotavirus ADIP (if GAVI decides to continue support).

In addition to the above meetings and videoconference, there would be ad hoc meetings or videoconferences with the Steering Committee. Presentations to the GAVI Board at its regularly scheduled meetings can also be arranged as needed to discuss key go/no-go decision points that require broader GAVI input.

E. Technical Review and Advisory Committee

A TRAC will also guide the ADIP. This committee will act as a strategic and technical advisory group to the ADIP team. This committee will be available to review RFPs for major grants (over US$500,000) and provide input on other technical and strategic issues as needed by the ADIP team. The TRAC will include a core group of four to five experts who will evaluate overall and specific ADIP plans and progress. This committee will convene annually in conjunction with the Steering Committee.

Due to the variety of projects and subject areas covered by the ADIP's scope of work, the core group of technical experts would be complemented, as needed, by individuals with expertise in the specific area under review. This would assure the program of a consistently high level of technical review and input. The Panel would include a GAVI Task Force member as appropriate by the content of the review as an observer to liaise back with the appropriate Task Force. Finally, the ADIP will work with other similarly tasked groups to combine functions when appropriate.

Approach to Issuing RFPs

One of the ways the ADIP would allocate funds and begin projects would be through RFPs. RFPs would be issued according to the needs identified in the annual workplan when appropriate. The ADIP team would assemble RFPs with input from the TRAC when necessary.

Many projects may not go through the RFP process and may be directly led by the ADIP team or consultancies. The TRAC would also be available to review these projects on an as-needed basis.

Project Review

The specific project applications and proposals for inclusion in the ADIP for Rotavirus Vaccines will be evaluated according to the following guiding principles. Each activity should explicitly advance a country or region towards vaccine introduction.

Proposals will be favorably viewed if:

- Activities are built off of present work without replacing funding or duplication.
- Available co-funding has been applied to enhance effectiveness at working toward the overall rotavirus goal.
- Countries selected for projects are likely to be early introducers of vaccine and/or are seen as trend-setters within the region.
- The work is deemed critical but is otherwise not being supported.

Projects should be able to answer the following questions:

- Is the data produced in this project necessary for decision makers to successfully introduce rotavirus vaccine?
- How does this project fit into the present landscape of rotavirus work?
- How does this project compress the timeline to vaccine availability?
- Does this project increase the knowledge of vaccine safety and efficacy needed for decision making?

Human Subjects Issues

All activities conducted under the ADIP's supervision or support that involve human subjects research will be handled according to internationally accepted guidelines. Each such project will require review and approval by an appropriately constituted Ethics Review Panel (ERP). Each institution participating in human subjects research sponsored by the ADIP will be responsible for ensuring that a qualified ERP reviews and approves the research before the research commences. If an institution does not host a qualified ERP, the review and decisions may be deferred to an acceptable ERP elsewhere. Research may also be reviewed by ERPs at organizations sponsoring the ADIP (e.g., WHO, CDC, etc.) depending on the circumstances. PATH's Human Subjects Protection Committee may review all protocols. A Federal-Wide Assurance will be obtained where appropriate. ADIP program managers will establish guidelines for this work during the first month of the Interim Management Team.

F. Building Collaborations With Key Partners

Beyond the partnerships with Primary Strategic Partners (WHO, CDC, and CVP), the ADIP team will need to work with other partners and align activities accordingly. Some of these partners are listed below. New partners may be included with the evolution of the workplan and the progression of the project from "Establishing and Communicating Value" to "Delivering Value."

Industry

The ADIP will strategically partner with industry to ensure the availability of vaccine to the developing world. These public-private partnerships will include the support of parallel clinical trials for multinational organizations and technical and financial partnering for emerging suppliers. Further, opportunities would be negotiated with industry after review by the ADIP Director and team members in consultation, as necessary, with the GAVI Steering Committee and/or TRAC.

Technical support for the ADIP team will be available through PATH's Business Development and Commercialization Group as needed to foster these relationships with industry partners.

Rotavirus Action Plan for Introduction and Development (RAPID)
The RAPID group is a creative partnership between industry and the public sector. This project has provided a forum for the public sector to interact with and influence industry as never before. Presently, RAPID is focused at ensuring parallel clinical trials in the developing world for at least one large multinational company. This work will compress the timeline for vaccine availability to the developing world. It includes several key partners, each investing in rotavirus work in a different way. These partners include the Center for Health and Population Research (formerly ICDDRB), USAID, NIH, CDC, WHO, CVP, and MEDUNSA.

ADIP team members are already members of the RAPID group and will ensure that RAPID projects are aligned with and included in the overall RAP, as well as representing ADIP projects to the RAPID group. The RAPID group will also be represented at ADIP annual meetings when interested parties are invited to participate.

Research and Development Task Force
The development of the ADIP concept has come directly from the work of GAVI's R&D Task Force. This task force has been given the difficult task of deciding upon the strategic new investments in research and development with regard to vaccines and immunization. This work has begun with a focus on rotavirus and pneumococcal disease.

The ADIP team will already report to a GAVI Steering Committee and will continue to interact with the GAVI Research and Development Task Force as needed. The Rotavirus ADIP team may be able to provide insights into the ADIP process as it gains experience, which may be helpful to future research and development activities.

Interactions With Ongoing Projects in the Field
The ADIP team will liaise with our partners' ongoing projects to update the overall RAP and link other possible future projects to the plan. In a similar way, the ADIP team will share results with partners, as these results may influence other rotavirus projects. The annual ADIP meeting with the GAVI Steering Committee will be designed to bring partners active in rotavirus work together for an add-on day to review ADIP and non-ADIP project progress and next steps.

V. PATH's Ability to Implement the ADIP

A. Experience in Managing Process or Team Similar to the ADIP

PATH is currently managing a US$245 million portfolio of vaccine development and introduction programs, including the Malaria Vaccine Initiative, the Meningitis Vaccine Project, and the Children's Vaccine Program (see Attachment N: Annual Reports from MVI, MVP, and CVP). All of these programs are managed within a team framework that emphasizes a high degree of independent decision making and encompasses extensive collaborative interactions with major international and multilateral partners. For example, MVP is managed within a joint partnership with WHO which requires extensive cross-connectivity and is governed by a Project Management Committee composed of an equal number of representatives from WHO and PATH. PATH has provided a focused and nimble administrative structure that has allowed MVP to pursue innovative strategies to develop meningitis vaccines for Africa and combines experience in business development with expertise in infectious diseases.

Over 15 years ago, PATH became the host to the Secretariat of the International Task Force on Hepatitis B Immunization, a team that within a ten-year period succeeded in placing global hepatitis B immunization within the EPI on the main agendas of WHO and UNICEF and was a catalyst in increasing the level of hepatitis B immunization in the developing world. One unique feature of PATH's management of this initiative was a governance structure in which the Task Force executive director reported not only to the president of PATH, but also to the chairman of an outside group of experts (the Task Force itself). This dual reporting requirement was governed by a Memorandum of Understanding between PATH and the Task Force. PATH managed the funds provided by the James S. McDonnell Foundation on behalf of the Task Force. The system worked extremely well over the ten years of the Task Force's existence and appears to be an already validated example of the type of management structure envisaged by the ADIP RFP. Through its experience with the Hepatitis B Task Force and CVP, PATH has a broad understanding of the barriers to vaccine introduction, the decision making process at the global and national level, and the lessons learned for moving forward.

B. Support PATH Brings to the ADIP Team

PATH brings extensive infrastructure support to the ADIP team:

Vaccine Research and Development

PATH has extensive experience with vaccine research and development including clinical trials. Much of this work is undertaken through the MVI, CVP, and MVP programs within PATH. Vaccine specific work includes Hib, Pneumo, Rota, and Malaria vaccines. A list of present ongoing projects is provided in Attachment S: PATH's Clinical Trials for Vaccines.

Vaccine Forecasting

Demand forecasting is key to influencing how the vaccine industry supplies vaccine. Historically, the public sector has not fully understood the importance of this task and the "demand" forecast has been confused with the "need" forecast. Through the work of Alan Brooks, CVP has been a leading force within the GAVI Financing Task Force to accurately forecast demand estimates for new and underutilized vaccines procured with The Vaccine Fund support. These efforts include estimating

demand for rotavirus vaccines. In addition, demand forecasts for meningococcal vaccines, malaria vaccines, and other PATH-supported technologies will be conducted at PATH over the next two years. There is a strong core of expertise in PATH's Business Development and Commercialization Group to design and implement these activities, with support from key consultants.

Vaccine Procurement

For over 20 years, PATH Procurement Services has worked with developing countries to facilitate their procurement of safe, effective vaccines at reasonable prices. This support consists of customized, in-country technical assistance, improving local capabilities so these countries can plan, implement, and monitor vaccine supply activities and systems. Our initial assessment of capabilities and constraints leads to the design and implementation of an individualized assistance program that addresses capacity development (training in international procurement procedures), vaccine quality, regulatory, financing, and logistics issues. The objective is to assist countries in establishing a sustainable and self-sufficient vaccine procurement system.

To support vaccine procurement training, PATH, in collaboration with WHO, produced a comprehensive vaccine procurement manual, *Procurement of Vaccines for Public Sector Programs* (published in 1999), that provides step-by-step guidelines on obtaining quality vaccine through international competitive procurement.

In addition to providing field technical assistance, Procurement Services supports PATH's health development projects in developing countries through the following services:

- Equipment and commodity sourcing;
- Material planning;
- Transportation management;
- Development of specifications;
- Strategies and planning for international tenders and other solicitation processes;
- Negotiating contracts and managing all logistical arrangements for delivery and customs clearance of goods; and
- Contract and project management services for high procurement component programs.

Procurement Services monitors organizational program trends and develops specialized buying programs for prominent initiatives, such as media and communications, diagnostic development support, major capital asset planning, and vaccine development program support.

For the MVI, and more recently, MVP which are tasked with bringing candidate vaccines through clinical trials to production, PATH Procurement Services has developed unique strategies for contracting specialized and complex research services. With the need to involve partner organizations in the final selection of contract service providers, Procurement devised and facilitated a solicitation and evaluation process to incorporate policy, programmatic, and technical interests of all organizations. This has ensured timely decisions and consensus building.

Business Development and Commercialization

PATH houses a highly competent business development team that provides intellectual property guidance, patent mapping capabilities, market assessment, financial feasibility study capability, and extensive industrial negotiating background. This team, together with its individual and institutional

consultants, provides assistance to all the Strategic Programs of PATH and will provide needed human resources to move the ADIP initiative forward. This team has already created the patent map for rotavirus vaccine candidates and has negotiated the public/private partnership agreement with the Indian producer for the new Indian rotavirus vaccine whereby this vaccine will be made available, once licensed, to the public sector in India. PATH has negotiated vaccine-related agreements with industry valued at over US$30 million in the last two years. Support from this team will be available to the ADIP team. Of particular importance is the extensive interaction this team has already had in business negotiation with one of the multinational manufacturers whose rotavirus vaccine candidate is targeted for interim ADIP support.

The underlying economics of the developing world vaccine market are insufficient to drive large pharmaceutical companies toward making their vaccines available in those markets. Thus, creative solutions that either change the economics or change the rewards to industry must be found in order to create a sustainable supply of vaccines and to encourage the development of new vaccines. The PATH Business Development and Commercialization Group excels in "low-leverage" negotiations, finding solutions that have enabled PATH to have several technologies commercialized, and striking deals with large vaccine manufacturers as well as with emerging suppliers. PATH is a credible partner to industry—both small and large companies—which demonstrates the ability to work in an innovative manner with industry.

Advocacy and Communications

From the beginning of GAVI, CVP has played a leading role in advocacy and communication for immunization. This expertise will serve the Rotavirus ADIP program well.

Different kinds of advocacy interventions will be necessary as the vaccine development and introduction process evolves. In the early stages, we will advocate with donors and potential donors, the scientific community, the pharmaceutical industry, and biotech firms to engage them in the process. The focus will be on resource mobilization, building a community of interest, and bringing additional partners—especially industrial partners—on board.

Later, during clinical trials, we will shift attention to the public, especially in the trial communities. The emphasis will be on raising awareness about rotavirus and communicating the importance of medical research. Once study results become available, dissemination of data to key partners, and future partners, will be important. When the vaccine is ready for introduction, coordinated advocacy, communication, and training initiatives will be necessary, targeting health workers, immunization program managers, and the consumers.

All these efforts will take advantage of many different media channels, depending on specific tasks. Work with the media will be crucial—especially as trials get underway.

C. Experience in Building Partnerships and Alliances, Especially Public/Private-Sector Partnerships

PATH has extensive experience building partnerships and alliances in both the public and private sectors. To document our experiences we have recently developed two key documents: PATH's Guiding Principles for Private Sector Collaboration (see Attachment O: PATH's Guiding Principles for Private Sector Collaboration and PATH's Guiding Principles for Achieving Programmatic

Impact) and Creating and Sustaining Effective Alliances: A Handbook for Collaboration (an internal draft). The principles for maintaining and sustaining effective public-sector collaborations, which would guide the ADIP team relationships with its Primary Strategic Partners, include the following: (1) communicate successes early and often, then sustain clear and frequent communication; (2) manage inherent dynamic tension between the public and private sector; (3) foster mutual accountability; (4) create partner equity; (5) apply crisis intervention when needed; (6) manage seconded staff effectively; and (7) manage organizational identity.

PATH's interactions with multilateral organizations such as WHO and UNICEF have been long-term. PATH has served and is serving as a WHO Collaborating Centre for Vaccinology, for AIDS, and for Human Reproduction. We partner directly with WHO in the Meningitis Vaccine Project, collaborate directly with UNICEF on communications and advocacy for immunization, and partner with the World Bank in work on immunization financing.

PATH has also engaged in a long list of partnership enterprises involving the private sector in both developed and developing countries. Contemporary examples include the nine vaccine development partnerships of PATH's MVI, all of which involve an industrial partner, including contract manufacturers, multinational pharmaceutical companies (big Pharma), and emerging suppliers; the two vaccine development projects of the MVP which involve alliances with big Pharma and an emerging supplier; and the PATH partnership with UNICEF, Becton Dickinson, and big Pharma in support of the use of tetanus toxoid in Uniject as part of the neonatal tetanus elimination campaign. PATH is also partnering with the Serum Institute of India in support of the advancement of new sugar stabilization techniques for vaccines.

We hold a fundamental belief that productive relationships with the public and private sectors can be created to develop and advance vaccines and technologies for the developing world. Our experience confirms it.

D. How the Rotavirus ADIP Team Would Fit Into PATH's Organizational Structure

The Rotavirus ADIP would be a Strategic Program within PATH's organizational structure (see Attachment P: PATH's Organizational Structure). In 2001, PATH implemented a significant reorganization, establishing the following nine Strategic Programs, which work closely with our field sites and serve as the management structure for programmatic activities:

- HIV and AIDS - PATH strengthens the foundation for a positive response to HIV and AIDS through activities that focus on behavior change at the individual and community level and technology solutions to prevent the spread of HIV and other sexually transmitted infection.

- Adolescent Health - Three major projects are housed in PATH's Adolescent Health Strategic Program. The African Youth Alliance is a partnership with Pathfinder International and UNFPA to scale up adolescent health programs in Ghana, Uganda, Botswana and Tanzania. The China Youth Reproductive Health Program, a partnership with the China Family Planning Association, is the first large-scale adolescent health program in China. The Entre Amigas project addresses the needs of 10- to 14-year-old girls in Nicaragua

- Gender, Violence, and Human Rights - The mission of PATH's Gender Violence and Rights Strategic Program is to promote gender equity in health and to prevent gender-based violence, using a systems approach to link policies, institutions, and communities.

- Malaria Vaccine Initiative - MVI's mission is to accelerate the development of promising malaria vaccine candidates and ensure their availability and accessibility for the developing world.

- Meningitis Vaccine Project - This partnership with WHO is aimed at eliminating epidemic meningitis as a public health problem in Sub-Saharan Africa through the development, testing, licensure, and widespread use of conjugate meningococcal vaccines.

- Children's Vaccine Program - The CVP works to ensure that all children receive the full benefits of new, lifesaving vaccines without undue delay.

- Technology Solutions - The primary goal of the Technology Solutions Strategic Program is to improve the health of women and children through the identification, adaptation, development, evaluation, advancement, and introduction of well-designed, affordable, and appropriate technologies for health, family planning, and nutrition.

- Reproductive Health - The current focus areas of this Strategic Program reflect reproductive health needs among women and men in the least developed regions of the world.

- Maternal and Child Health and Nutrition - The Maternal and Child Health and Nutrition Strategic Program addresses health and nutrition issues on the continuum of care for women of reproductive age and newborn babies through childhood.

The directors of these Strategic Programs report directly to the president of PATH (unless he delegates that responsibility to another member of PATH's Executive Leadership Team, which is composed of PATH's six vice-presidents). PATH's Administration, Finance, and Human Resources department serves each of the Strategic Programs. Staff of the Strategic Programs work in partnership with other PATH sites and across disciplines to share new ideas, technologies, and approaches in a continuous effort to achieve a maximum impact and lasting results. The directors of the Strategic Programs, although working within the matrix of an overall management and accountability structure, have extensive delegated authority to manage the programs under their responsibility. If awarded, the ADIP for Rotavirus Vaccine will be a new Strategic Program, with the director reporting directly to the president of PATH. PATH's senior vice president and medical director will also serve as a senior institutional advisor to both the Director and the Scientific Director of the ADIP.

While the Rotavirus ADIP would be a Strategic Program of equal and independent status to CVP, it is anticipated that the two programs would closely collaborate, hence CVP's designation as a Primary Strategic Partner of the ADIP.

E. Ability to Work Within a Project Milestone Framework

PATH works within project milestone frameworks for its product development activities. This framework ensures that goals are clear to all partners and that the project stays on track for its original purpose or is changed with the deliberate and explicit agreement of partners. For example, MVI has nine vaccine development partnerships—all with clearly identified governance structure, milestones, and go/no-go decision points. MVP has just concluded an extensive effort to develop a product development plan with key activities, milestones, and go/no-go decision points for a vaccine development partnership involving three commercial partners. Additionally, CVP is supporting the development of a rotavirus vaccine in India under the auspices of the US-India Vaccine Action Plan. Considerable effort has been invested in developing and agreeing on project gantt charts and critical milestones with go/no-go criteria.

A governance structure is critical to manage collaborative projects undertaken in a project milestone framework. PATH adopted an industry best practice by organizing Joint Vaccine Development Committees with each of its major industry partners. These are lean, empowered decision making structures that deal with the inevitable alterations and setbacks inherent in development work with biologicals. For example, one of the MVI's Joint Vaccine Development Committees has been in place for over two years and has dealt efficiently with issues ranging from dose selection to an unexpected change in clinical trials sites.

F. Financial Management, Logistics, and Administrative Capabilities

Financial Management

PATH has been part of the global health community for 25 years, and we have developed a robust financial management system to administer project awards. PATH currently manages an annual budget of over US$80 million, with awards coming from multiple funding organizations. Our financial management system is staffed by qualified professionals who provide internal controls that maintain organizational integrity and meet the requirements for individual awards. PATH is respected for its success in financial management, which has allowed our continued growth and expansion in a multiple-funder environment. The Association of PVO Financial Managers has commended PATH for its well-executed, robust administrative systems. This overall financial management system provides the structure and resources for individual project financial management. PATH is audited annually by an outside certified public accounting firm, which has consistently issued clean audit opinions (see Attachment Q: PATH's Audit Letter).

Logistics

Capabilities in Meeting Organization and Logistics

PATH has extensive experience in planning, organizing, and managing large meetings, both domestically and internationally. With many overseas sites, PATH offers local expertise and support in coordinating large meetings throughout the world; we arrange several international meetings annually. A few examples are offered to illustrate PATH's history of meeting preparation. PATH was the primary organizer of the International Symposium on Hepatitis B Immunization held in Yaounde, Cameroon, in 1991, which was attended by more than 150 participants from dozens of countries. More recently, PATH Ukraine staff played a key coordinating role in the June 2001 meeting on hepatitis B and immunization systems strengthening convened in St. Petersburg, Russia. PATH Mekong contributed technical assistance and provided logistical support to the coordination of the GAVI SEARO-WPRO Japanese Encephalitis Meeting held in Bangkok, Thailand, in June

2002. PATH has coordinated several meetings for GAVI, including the critical July 1999 meeting that established the current Alliance as well as the GAVI Working Group Meeting held in PATH's Seattle office in November 2001.

PATH's facilities include state-of-the-art audio-visual equipment and the capability to host over 130 participants. PATH also has video-conferencing equipment to bring staff and participants together when travel may not be possible or necessary. PATH staff can quickly and efficiently carry out all tasks to conduct an international meeting, from the initial invitations through the publication of meeting proceedings. Our Travel Coordination team and other staff regularly provide assistance with hotel reservations for all staff, as well as travel arrangements for supported participants. Our flexibility and speed is demonstrated in the ability to develop and distribute meeting materials and documents that may not be available until quite late in the planning process. In Seattle and abroad, PATH has access to a large number and variety of service providers for lodging and catering, and our past record with these vendors aids in ensuring happy participants. PATH meetings and special events are occasions that often include colleagues from all over the world, and feature receptions that allow staff and other local guests to become better acquainted or discuss side topics of interest. These receptions often have guest lists in the hundreds, including donors and public health professionals.

Travel

PATH has a travel team dedicated to handling the travel arrangements for 166 PATH Seattle-based staff and approximately 100 others annually. PATH has a travel agent dedicated to PATH travelers who is adept at complex international travel and changing itineraries. The in-house travel team coordinates hotels, arranges visas, and completes the paperwork for approvals, travel advances, and reimbursement. Approval for travel is done at the level of the team leader—so trips, depending on their complexity, can be arranged in one day and travel advances can be expedited within one to two days.

Administrative

Contracting

PATH has substantial experience managing subordinate agreements (see Attachment R: Contract Examples). Strong internal systems are in place to ensure adherence to a competitive bid process, to monitor agreement performance, and to track the status of financial and narrative reports. Over the past five years, PATH has written, managed, and monitored over 750 subordinate agreements totaling $70 million for activities in over 65 countries.

PATH uses a range of agreement instruments to ensure that the terms appropriately reflect the goals and objectives of PATH's donors while tailoring the provisions to be appropriate to the activity. Most of PATH's subordinate agreements are issued as grants, collaborative agreements, or contracts, but PATH will also adapt its systems as necessary to carry out program objectives.

Using the underlying principle of protecting the interests of the public sector as a guide, PATH's management approach balances efficiency and due diligence.

To be flexible and responsive to contracting needs, PATH establishes a team for each project with expertise to assess and address issues in business development, risk analysis and agreements,

technology and program implementation, and program administration. This dedicated team applies lessons learned from previous vaccine-related projects and agreements to new partnerships, which enhances issue analysis and streamlines the effective placement of agreements. While complex vaccine development agreements can take months to negotiate, based on the availability of the partners, straightforward agreements can be placed in as little as a week with complete information.

Prior to entering into an agreement, PATH will evaluate the reputation and economic stability of the prospective collaborator and assess its scientific and technical capabilities. Risk is mitigated through due diligence in selection of partners and carefully written agreements that codify objectives and contain appropriate indemnification and enforcement provisions.

Collaborative agreements always include clearly stated objectives, roles and responsibilities of each partner, and a decision making structure. Accountability and performance milestones and a clearly stated process for monitoring and evaluation ensure that goals are met.

A key element in the development and introduction of new technologies is PATH's collaboration with private-sector companies. Prior to entering into such a collaboration, PATH will evaluate the likelihood that such a collaboration will result in increased availability, accessibility, and affordability of key technologies or products in developing countries. PATH strives to balance the collaborator's commercial objectives with PATH's mandate to serve the public good. While the collaborator's need for confidentiality is respected, PATH reserves the right in all agreements to disclose the existence and purpose of the collaboration.

Recruitment of the ADIP Team and Compensation

Throughout its history, and especially during the past few years of major growth, PATH has repeatedly demonstrated its ability to quickly and flexibly recruit staff at all levels for new programs, including the Children's Vaccine Program, the Malaria Vaccine Initiative, and the Meningitis Vaccine Project. The average time for recruitment and selection for the directors of these programs was slightly more than 45 days, with candidates joining PATH one to three months after acceptance of their respective appointments. PATH staff has almost doubled over the past three years, increasing from 241 employees to 450 employees. Building Human Resources staffing capacity concurrently to manage this growth has been a priority and has enabled PATH to recruit efficiently and effectively. The internal approval process is streamlined and involves only two layers in the organization, the team leader and the Human Resources Unit (comprising the director of Human Resources; the vice-president of Administration, Finance, and Human Resources; and the president). This allows us to rapidly establish positions and initiate the recruitment process.

Once approved, a position is posted on PATH's web page of job opportunities and other effective Internet sites, such as the American Public Health Association's Career Mart, the Communication Initiative, Global Health Council's Career Connections, the Technet21 e-Forum on immunization services (supported by WHO and UNICEF and hosted in cooperation with the Center for International Cooperation in Health and Development), and the Public Health Employment Connection at Emory University's Rollins School of Public Health. In addition, PATH has an extensive employee referral network that alerts public health professionals to career opportunities at PATH. PATH is an equal opportunity and affirmative action employer.

The following Recruitment Grids show the average time for recruitment for CVP, MVI, and MVP program directors and other key professional positions.

Recruitment Grid

Position	Date Posted	Acceptance Date	# Months Post to Hire
CVP Director	9/98	10/98*	1
MVI Director	7/99	9/99	2
MVP Director	5/01	7/01	2
			1.7 Average

*Dr. Kane fulfilled position responsibilities as WHO staff until he retired from CDC and joined PATH in July 1999.

Others Key Professional Positions:

Position	Date Posted	Acceptance Date	# Months Post to Hire
PATH Communications Director	1/01	3/01	2
Vice President - Field Site Coordination	11/01	4/01	5
Testing Engineer	5/02	8/02	3
Meningitis Vaccine Project Senior Program Officer	4/02	7/02	3
Project Administrator	6/02	8/02	2
Technical Writer	7/02	8/02	1
			2.7 Average

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