

R. Ashton

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PROJECT PAPER

INDIA: Vaccine and Immunodiagnostic
Development (386-0503)

April 8, 1987

UNCLASSIFIED

PROJECT PAPER

VACCINE AND IMMUNODIAGNOSTIC DEVELOPMENT

AGENCY FOR INTERNATIONAL DEVELOPMENT PROJECT DATA SHEET	1. TRANSACTION CODE: <input type="checkbox"/> A = Add <input type="checkbox"/> C = Change <input type="checkbox"/> D = Delete	Amendment Number _____ DOCUMENT CODE 3
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2. COUNTRY/ENTITY India	3. PROJECT NUMBER 386-0503
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4. BUREAU/OFFICE Asia/Near East	5. PROJECT TITLE (maximum 40 characters) Vaccine and Immunodiagnostic Development
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6. PROJECT ASSISTANCE COMPLETION DATE (PACD) MM DD YY 08 30 93	7. ESTIMATED DATE OF OBLIGATION (Under 'B' below, enter 1, 2, 3, or 4) A. Initial FY 87 B. Quarter 4 C. Final FY 89
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8. COSTS (\$000 OR EQUIVALENT \$1 =)						
A. FUNDING SOURCE	FIRST FY 87			LIFE OF PROJECT		
	B. FX	C. L/C	D. Total	E. FX	F. L/C	G. Total
AID Appropriated Total	3,000		3,000	6,000		6,000
(Grant)	(3,000)	()	(3,000)	(6,000)	()	(6,000)
(Loan)	()	()	()	()	()	()
Other U.S.		2,000	2,000	4,000		4,000
1. A.I.D. S&T Bureau						
2. Public Health Service		456	456		1,621	1,621
Host Country		1,000	1,000		7,000	7,000
Other Donor(s)						
TOTALS	3,000	3,456	6,456	10,000	8,621	18,621

9. SCHEDULE OF AID FUNDING (\$000)									
A. APPROPRIATION	B. PRIMARY PURPOSE CODE	C. PRIMARY TECH. CODE		D. OBLIGATIONS TO DATE		E. AMOUNT APPROVED THIS ACTION		F. LIFE OF PROJECT	
		1. Grant	2. Loan	1. Grant	2. Loan	1. Grant	2. Loan	1. Grant	2. Loan
(1) HE	B511	970		-	-	3,000	-	6,000	-
(2)									
(3)									
(4)									
TOTALS				-	-	3,000	-	6,000	

10. SECONDARY TECHNICAL CODES (maximum 6 codes of 3 positions each) 550	11. SECONDARY PURPOSE CODE
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12. SPECIAL CONCERNS CODES (maximum 7 codes of 4 positions each) A. Code BR R/H B. Amount	
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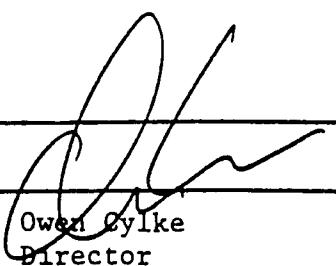
13. PROJECT PURPOSE (maximum 480 characters)

To develop vaccine to expand the range of diseases that can be prevented by immunization programs and to develop accurate, inexpensive diagnostic technologies for use in the Indian health care system to improve the quality of patient care and to generate valuable epidemiologic information which will be essential in improving the efficiency of immunization programs.

14. SCHEDULED EVALUATIONS Interim MM YY MM YY Final MM YY 08 88 06 92	15. SOURCE/ORIGIN OF GOODS AND SERVICES <input checked="" type="checkbox"/> 000 <input type="checkbox"/> 941 <input type="checkbox"/> Local <input type="checkbox"/> Other (Specify)
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16. AMENDMENTS/NATURE OF CHANGE PROPOSED (This is page 1 of a _____ page PP Amendment.)

Special Note: In the event that an activity is identified that could have a negative environmental impact, both USAID and the Government of India will strictly observe the applicable environmental regulatory requirements.

17. APPROVED BY	Signature  Title Owen Glyke Director	Date Signed MM DD YY 4/8/87	18. DATE DOCUMENT RECEIVED IN AID/W, OR FOR AID/W DOCUMENTS, DATE OF DISTRIBUTION MM DD YY
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GLOSSARY

- Acellular** - Not containing intact cells or parts of cells; this implies something which is a product, not a part of a cell.
- Antibody** - A protein naturally existing in blood serum or produced in response to stimulation by an antigen, that reacts to overcome the toxicity of a specific antigen.
- Antigen** - Any of a class of substances that stimulate production of antibodies.
- Assay** - Determination of the purity of a substance or the amount of any particular constituent of a mixture.
- Attenuate** - To weaken or reduce in force, intensity, effect, quantity, or value.
- Auxotrophic** - Having growth factor requirements differing from those of the ancestral or prototype strain.
- Biotechnology** - The development of biological forms and systems for obtaining maximum benefits to man and other forms of life by the use of conventional and novel techniques of interaction between living and living as well as living and non-living.
- Circumsporozoite** - Referring to the material which surrounds or ensheathes the sporozoite stage of the malaria parasite cycle. Some of this material is antigenic.
- DNA** - (Deoxyribonucleic Acid) The genetic material found in all living organisms. Every characteristic of every living organism can be traced to the code of its DNA.
- Enteric** - Pertaining to the intestines.
- Epitope** - Simplest form of antigenic determinant present on a complex antigenic molecule.
- Hemagglutinin** - A substance that causes agglutination of red corpuscles.
- Hybridization** - The act or process of producing hybrids, which are the progeny of parents of two different species, types, or traces.

- Hybridoma - A cell line created by crossing a rapidly growing tumor cell with a non-tumor cell which has the capacity to produce an antibody.
- Immunodiagnosis - Diagnosis by use of an antibody to react with and identify a specific disease antigen in a patient's serum, saliva, urine or stool.
- Immunosorbant - The characteristic of a substance which has the capacity to hold an antigen or antibody for a reaction with its opposite.
- Monoclonal Antibody - Antibody produced by the progeny of a single hybridoma cell. That progeny which is all descended from a single cell and shares identical genetic material is called a clone.
- Oligopeptide - A compound made up of very limited number of amino acids.
- Pathogen - Any disease producing microorganism or material.
- Peptide - A compound containing amino acids, made synthetically or formed by the hydrolysis of proteins.
- Polypeptide - A compound containing two or more amino acids and one or more peptide groups.
- Polysaccharide - One of a group of carbohydrates that contain more than four molecules of simple carbohydrates combined with each other.
- Reagent - A substance employed to produce a chemical reaction.
- Recombinant DNA - As a process: The combination of DNA from different organisms in vitro. As a product: Hybrid DNA produced by combining new or foreign DNA with host DNA at the molecular level.
- RNA - (Ribonucleic acid). The nucleic acid responsible for decoding genes.
- Seroepidemiology - The study of the spread of a disease or the effectiveness of a vaccine by analysis of serum antibodies in a population under observation.
- Serology - The study of antigen - antibody reactions in vitro.

- Toxoid** - A toxin rendered nontoxic by treatment with chemical agents or by physical means and used for administration into the body in order to produce specific immunity by stimulating the production of antibodies.
- Valent** - A suffix meaning "having worth or value."

DEFINITION OF ACRONYMS

- AID - Agency for International Development (U.S.)
- CDC - Centers for Disease Control (U.S.)
- CERT - Centre for Epidemiological Research and Training (India)
- DBT - Department of Biotechnology (India)
- ICMR - Indian Council of Medical Research (India)
- JWG - Joint Working Group
- MOU - Memorandum of Understanding
- NIAID - National Institute of Allergy and Infectious Diseases (U.S.)
- NIH - National Institutes of Health (U.S.)
- PASA - Participating Agency Services Agreement
- PHS - Public Health Service (U.S.)
- UNICEF - United Nations International Children's Emergency Fund
- VAP - Vaccine Action Program
- VIDX - Vaccine and Immunodiagnostic Development
- WHO - World Health Organization

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PROJECT PAPER
VACCINE AND IMMUNODIAGNOSTIC DEVELOPMENT

I. Executive Summary

While the health status of the Indian people has improved significantly over the past several decades, health prospects in India remain a cause for serious concern. In an effort to increase its effectiveness in curbing morbidity and mortality rates, the Government of India (GOI), in 1980, revised its health care strategy to place an increasingly heavy emphasis on preventive health care measures.

Of the known preventive health care technologies, vaccines are the most cost effective. Diagnostic techniques are also critical to preventive health care. Accurate diagnoses of disease generates epidemiologic information that is essential to planning and implementing disease control programs.

As a result of exciting breakthroughs in biotechnology, vaccines and diagnostic techniques that would not have been possible just a few years ago are now technically and commercially viable. Recognizing the potential created by the breakthroughs, India is positioning itself to be an active force in the biotechnology revolution. The country has both the technical manpower and the political will to be successful in this venture.

India's commitment to biotechnology will accelerate the rate of research results that have a direct application to developing countries and will permit India's science community to have an impact that reaches far beyond the geographical borders of the country. This is particularly true in the field of immunology. Conditions in India and other developing countries differ from those in developed countries where immunization programs have been most successful and where the bulk of medical research takes place. For instance, malnourished children do not respond as well to vaccines and, often, require increased dosages of immunization. Vaccines need to be more heat stable in developing countries because cold chains are more difficult to maintain. Combinations of vaccines are necessary to simplify immunization programs and to achieve maximum coverage. The duration of protection must be increased to cover individuals who, for whatever reason, are unable to return for booster shots.

New vaccines need to be developed for diseases that contribute heavily to morbidity and mortality in developing countries and for which there are no safe, effective vaccines available. Vaccines for several of these diseases are in the development pipeline and technological breakthroughs are expected in the foreseeable future.

Finally, improved diagnostic techniques are required to ensure, for the individual, that specific, effective treatment for the

illness is provided and, for the health planner, that information is available on which to base the selection of disease prevention and control measures, evaluate community health status, and assess the impact of interventions. These diagnostic techniques must be simple and rapid and take into account the limitations of the equipment and technical staff in the field where the techniques will be administered.

To assist the Government of India achieve its medical research objectives, USAID proposes a six year, \$6 million project, Vaccine and Immunodiagnostic Development (VIDX). The first and major component of the project will provide \$4,650,000 to sponsor Indo-U.S. collaborative research to develop and test vaccines and diagnostic techniques for selected viral, bacterial, and protozoal diseases. The second component will provide \$1 million to support the field trials of a recently developed synthetic peptide vaccine against the most deadly form of human malaria, P. falciparum. The third component will contribute \$250,000 to support the Indian Centre for Epidemiological Research and Training, an institution being created to facilitate the field testing of new medical technologies. Approximately \$100,000 has been set aside for project evaluation.

The project builds on Indo-U.S. scientific relationships established under the U.S. Public Health Service program and is part of a broader Indo-U.S. effort designed to support vaccine research, production, quality control, and delivery methodology. This broader effort, which will involve the Department of Biotechnology (DBT), the Ministry of Health and Family Welfare (MOHFW), and the Indian Council of Medical Research (ICMR) on the Indian side and the U.S. Public Health Service (PHS) and the Agency for International Development (AID) on the U.S. side is known as the Vaccine Action Program (VAP). VIDX project outputs will include:

new and improved vaccines to extend the range of diseases that can be effectively prevented through immunization;

new and improved immunodiagnostic technologies to improve the efficacy of patient care and to make seroepidemiologic surveys of vaccine preventable diseases feasible so public health planners can develop practical disease control strategies;

Indian scientists and technologists familiarized with the most current research and epidemiological methodologies that are germane to vaccine and immunodiagnostic development, disease surveillance and quality control of vaccine manufacture;

II. Background and Project Rationale

A. Burden of Vaccine-Preventable Diseases in India

The health status of the Indian people has improved significantly over the past several decades. The mortality rate per thousand

of population has declined from 27.4 (1942-52) to 11.9 (1984); the infant mortality rate per thousand live births has declined from 161 (1941-45) to 105 (1982); and life expectancy at birth has increased from 32.45 to 54.1 years in thirty years (1951-1981). Today the Indian life expectancy at birth averages over 55 years.

Despite these gains, health prospects in India remain a cause for serious concern. Children are particularly at risk. It was estimated in 1977 that, although children under five years of age constituted less than fifteen per cent of the total population, they represented almost half of the total deaths in the country each year. One in every ten newborn Indian babies does not live to celebrate his first birthday. The situation is especially discouraging in the rural areas where the infant mortality rate is 76 percent higher than in urban areas.

Of the top twenty causes of infant mortality in India, four fall under the category of respiratory diseases and three under the category of diarrheal diseases. Only prematurity claims more lives.

Approximately four million cases of serious lower respiratory disease occur each year in India. An estimated ten percent of these cases result in death. This works out to 400,000 deaths per year or 1100 deaths per day. In 1978 the mortality rate in India for respiratory diseases among children under one year of age was 2,707 per 100,000 children. The comparable rate in the United States was 54 per 100,000 children.

There are almost ten million cases of diarrheal disease reported annually in India. An estimated ten per cent of all infant deaths are attributed to diarrheal diseases. Even when the disease does not result in death, there are significant consequences. For days and weeks after a diarrheal episode, absorption of nutrients can be hampered. Malnutrition predisposes an individual to diarrhea and diarrhea in turn fosters malnutrition. In many cases children's growth is stunted in developing countries by nutritional deficiencies created during the malnutrition-diarrhea-malnutrition cycle.

Other diseases, such as hepatitis, typhoid, and malaria, have high rates of incidence among adults as well as children. While not major killers in India, they weaken the individual and increase his susceptibility to other infections. This interaction of infections combined with other factors such as nutritional deficiencies can have a cascading effect, often leading to serious disabilities, if not death. Thus, attention to these less fatal diseases is necessary not only to reduce the morbidity and mortality attributable to the diseases themselves, but to effect also an impact on morbidity and mortality indirectly associated with them.

Of the diseases mentioned above, malaria is particularly worrisome. Reported incidence of the disease in 1984 was 18 percent higher than in 1983. Incidence of the deadly P. falciparum strain registered an increase of almost 13 percent.

B. Opportunities Provided by Vaccines and Rapid Diagnostic Techniques

Vaccines are the most effective health care technologies available. They are responsible for the eradication of smallpox and, to a great extent, for the low rate of infant mortality in the developed world. Judged against other preventive measures, such as altering environmental conditions or changing human behavioral patterns, vaccines represent a proven intervention well within the capacity of the Indian health system to deliver. Moreover, vaccines are cost effective. The Indian government estimates that it can immunize a child against diphtheria, pertussis, tetanus, poliomyelitis, tuberculosis and measles for a little more than \$3.00, well under the cost of treatment for any one of these diseases.

Biotechnology has created a potential for vaccine development that technically and economically would not have been feasible just a few years ago. The necessary ingredient for the development of any new vaccine is the availability of the living organism or of the key antigens in the organisms against which immunity can be directed. Six years ago such antigens were not available for many vaccines and scientists, for the most part, believed there was a serious limitation on the number of future vaccines that could be produced. This pessimism was dispelled by biotechnological breakthroughs in antigen identification and preparation by 1) recombinant based DNA production of proteins and polypeptides, 2) production of synthetic oligopeptides and monoclonal antibodies by hybridoma technology, and 3) directed mutation, selection and stabilization. As a result of these breakthroughs, several vaccines that are especially relevant to developing country needs are now at various points in the technology development pipeline. Below is a list of some of the vaccines that have the potential to relieve the burden of disease in India and an indication of each vaccine's stage of development.

Genetically engineered strains of V. cholerae which produce an asymptomatic infection that confers protection against the disease are undergoing initial clinical safety trials. These oral vaccines could be incorporated without difficulty into immunization programs.

Several efficacy trials of a live attenuated oral typhoid vaccine (Ty21a) have produced varying results to date. While these trials are being continued, other oral attenuated typhoid vaccine strains are under development. Some of the newer vaccines incorporate recombinant DNA technology to produce "cocktail" enteric disease vaccines, including

prototypes combining typhoid and *Shigella* and typhoid and cholera antigens.

Efficacy trials of live attenuated rotavirus vaccine derived from bovine and rhesus monkey sources are underway in several locations with AID, NIH and WHO support. These vaccines are expected to be administered orally with polio vaccine to infants.

Clinical efficacy trials are underway of a new hepatitis B vaccine which utilizes recombinant DNA technology to express protective antigens in yeast or mammalian cells. This vaccine will replace expensive vaccines formulated from inactivated hepatitis B virus surface antigen derived from human plasma.

A prototype live attenuated hepatitis A virus vaccine is ready for Phase I studies in man.

Recent advances have been made in the development of oral rabies vaccines through the application of recombinant DNA technology and vaccinia virus vectors.

Two acellular pertussis vaccines, a purified single component (toxoid) and a two-component (toxoid plus filamentous hemagglutinin) product are currently being tested with AID and NIH support in Sweden. If the new vaccines are at least as effective and cause fewer adverse reactions than the current whole-cell vaccine, they will be in demand for immunization programs throughout the world.

A *Hemophilus influenzae* type B capsular polysaccharide vaccine for the prevention of meningitis, epiglottitis, and pneumonia has been licensed recently in the U.S., but it is not used widely in universal immunization programs. This vaccine is not effective in infants and young children, the primary target population for pneumonia vaccines, but is effective in children two years of age and older.

A protein-polysaccharide conjugate (diphtheria toxoid plus PRP) *Hemophilus influenzae* type B vaccine for use in children under two years of age is currently being tested on Alaskan children. If these trials are successful, a vaccine will be available which will protect infants and young children in whom pneumonia is a common life-threatening illness.

Two recombinant DNA-derived antigens for the circumsporozoite protein of the malaria parasite, *P. falciparum* will undergo the first human safety studies soon. These will be the first clinical studies of a major vaccine-development program. Additional antigens directed against other *Plasmodium* species will

emerge from the development pipeline in the next six to twelve months, some of which will result from novel recombinant DNA techniques.

Improved rapid diagnostic techniques are also critical to upgrading the health status of the Indian people. Traditional laboratory diagnostic technologies involve: 1) direct examination of specimens or cultures of blood, stool, urine, sputum, or tissue biopsy using simple equipment and reagents, or 2) immunologic techniques, including the detection of antibodies produced by the patient in response to an infection and the use of antibodies as reagents to detect antigens of the pathogen or other evidence of infection in patient specimens. The non-immunologic techniques, though often inexpensive, generally require specially trained personnel, are time-consuming, and frequently fail to detect evidence of infection. The immunologic techniques have significant advantages over the direct techniques, but to utilize these techniques, technicians must be retrained and supplied with specialized equipment and reagents.

Newer immunodiagnostic methods, including monoclonal antibody and DNA or RNA hybridization technologies, are equally as exciting as the recent advances in vaccine research and offer hope of rapid, simple, highly accurate, and inexpensive tests that can be performed with crude specimens under field conditions. The accurate diagnoses produced by these techniques will benefit both the individual being treated and the health professionals responsible for surveillance and health services planning. Promising areas for research in rapid immunodiagnostics include but are not limited to:

An enzyme-linked immunosorbant assay (ELISA) for malaria using monoclonal antibodies;

DNA and RNA hybridization test for malaria and for the identification of diarrheal diseases such as rotavirus and E. coli;

Detection and identification of respiratory disease pathogens using latex agglutination and other solid phase materials;
Detection of bacterial polysaccharide antigens such as the Vi antigen to diagnose a case of typhoid fever and pneumococcal capsular antigens as a low-cost alternative to blood culture diagnosis.

C. Relationship of Project to AID Strategy

In September 1983, USAID adopted a ten year development-oriented strategy for Indo-U.S. collaboration in research and technology development. The strategy reflects the AID conviction that support for research and technology development is essential for sustained improvement of productivity and well-being of the people. One of the areas targeted in the strategy for AID program development

is biomedical research. This project is responsive to the USAID science and technology development strategy and supports the strategy objectives of enhancing the institutional research capabilities of Indian scientists and institutions and promoting Indo-U.S. scientific collaboration in areas of mutual concern to both countries.

Although an outgrowth of the S&T strategy, the project is complementary to the portfolio of the Health and Nutrition Office. A significant portion of project resources will support the achievement of USAID/India's approved health sector goal, i.e., a reduction in infant and child mortality.

The chief causes of infant mortality in India are prematurity, respiratory infections, and diarrheal diseases. Research to identify and develop interventions to reduce the incidence of prematurity is being sponsored under the Integrated Child Development Services project. One of the known causes of prematurity is inadequate child spacing. Research to provide an alternative to existing spacing methods is being conducted under the Contraceptive Development: Reproductive Immunology Project. The research gap, which the proposed project fills, is on vaccines and diagnostic techniques that will address the morbidity and mortality associated with respiratory infections, diarrheal diseases, and other major diseases in India.

The proposed project will directly complement the recently initiated Biomedical Research Support Project which is designed to assist the Indian Ministry of Health and Family Welfare's National Institute of Communicable Diseases create a functioning program of laboratory based field epidemiology with its concomitant emphasis on preventive medicine. The rapid diagnostic technologies to be developed and tested under the proposed project will be incorporated into the epidemiological program being established under the Biomedical Research Support Project. Epidemiological capabilities to be developed at the Indian Council of Medical Research's Center for Epidemiological Research and Training under the proposed project will be supportive of and complementary to those capabilities being developed at the National Institute of Communicable Diseases under the Biomedical Research Support Project.

Finally, the proposed project is linked to another FY 1986 start, Child Survival Support. An important thrust of the Child Survival Support Project will be the delivery of immunizations along with a creation of demand for immunizations among the rural poor. The Child Survival Support Project could support operational research in the delivery and use of technologies developed under the proposed project.

D. Relationship to Host Country Strategy and Capabilities

1. Host Country Commitment to Biotechnology

The Indian Government has identified biotechnology as an emerging science area of highest importance. In 1982, it created the

National Biotechnology Board to identify priority research areas, to initiate and fund R&D programs in both public and private laboratories, and to coordinate biotechnology activities nationwide. In 1986, the Board was elevated to the status of department*.

The Department of Biotechnology has devoted considerable resources to expanding and upgrading both the manpower and the physical facilities of laboratories involved in biotechnology. It has also set up a central facility to procure and produce critical inputs required for biotech research such as enzymes and radionucleotide labelled probes.

In 1983, the Long Term Plan in Biotechnology for India was issued. Among the areas identified in the plan for highest attention are:

the development/production of vaccines against major viral, bacterial and protozoal diseases using modern methods of animal cell/tissue culture and genetic engineering; and,

the development of diagnostic kits based on enzyme-linked-immuno-assay (ELISA) procedures which will facilitate accurate diagnosis of various disease of man and animals.

About fifty Indian institutions are engaged in biotechnology research and development work. In the health area, publically funded laboratories such as the Delhi-based Institute of Immunology and the All-India Institute of Medical Sciences are in the vanguard. The private sector, led by the Tata Research Design and Development Centre, is also making significant investments in biotechnology research and development. The primary area of interest within these institutions is advanced research on vaccine and diagnostic kits.

2. Host Country Commitment to Immunization

The Government of India is committed to bringing down morbidity and mortality rates. Moreover, as it clearly states in a 1980 policy document, Health for All: An Alternative Strategy, it believes that preventive measures can have a considerable impact on that goal. Immunization is recognized as the most cost effective of the preventive interventions and the GOI has a long history of supporting vaccine delivery programs. Vaccination against tuberculosis and smallpox was introduced on a widespread scale in the sixties. In 1978, the Government of India adopted the Expanded Program for Immunization with the objective of providing a package of vaccines to

*Further underscoring the GOI's commitment to biotechnology, was the intensity with which it pursued having India named as a site for the UNIDO Biotechnology Center. As a result of successful lobbying and a commitment of support approaching \$20 million, the center will be located in Delhi.

children under five and to pregnant women. In 1985 the government intensified its vaccination effort with the announcement of the Universal Immunization Program. Under the universal program, India hopes to achieve immunization coverage of the entire eligible population (children and pregnant women) by 1990. The tasks involve immunizing 18 million newborns and 22 million expectant mothers every year.

III. Project Description

A. Goal

The project goal is to reduce morbidity and mortality in India, particularly among infants and children.

B. Purpose

The project purpose is to develop vaccines that will expand the range of diseases which can be prevented by immunization programs and to develop accurate, inexpensive diagnostic techniques for use in the Indian health care system to improve the quality of patient care and to generate valuable epidemiologic information which is essential in improving the efficacy of immunization programs.

C. Project Components

1. Project Component One: Research Awards Program

Bench, clinical, and field research to develop new and improved vaccines and rapid diagnostic techniques will be sponsored under this component of the project. The research proposals, or protocols, will be jointly developed and carried out by Indo-U.S. collaborators, both from the public and private sectors. The protocol review and approval process is described in Section IV of this paper entitled "Project Implementation."

Priority disease areas that will be eligible for research support under the project were identified jointly by Indian and U.S. scientists and public health experts at the Indo-U.S. Science and Technology Sub-Commission meetings held in April 1985 and at VAP meetings held at NIH March 31 - April 2, 1986. These priority areas could change in succeeding years of the project as other areas of research opportunity are identified. In selecting priority disease areas, consideration was and will be given to the seriousness of the threat posed by the disease to the Indian population, the potential for near term success in developing a vaccine or diagnostic technique, and the level of interest in the disease areas on the part of Indian and American scientists. The priority disease areas with which the project is likely to begin are described below.

Cholera is a serious epidemic diarrheal disease in India and in other parts of Asia for which oral rehydration therapy is ef-

fective but for which no effective preventive measures exist. Oral vaccines formulated from killed whole organisms and purified cholera toxin subunits (which act as toxoids) have recently been shown to induce high levels of protective immunity, but the duration of the protection is not known. Newer live attenuated cholera strains which mimic natural infection (which confers high level, long lasting immunity) offer real prospects to improve the efficacy of cholera vaccines. Collaborative research of new and emerging candidate strains through the application of recombinant DNA research will be eligible under the project.

Typhoid fever is a common serious enteric infection in India and elsewhere in developing countries. Research related to typhoid and field trials of both the new Vi antigen injectable vaccine and oral attenuated vaccines, which are under development in the U.S., will be eligible for support. The latter category of vaccines are auxotrophic mutant strains which act against typhoid fever alone and as carriers of antigens of other enteric pathogens as combination or "cocktail" vaccines developed through recombinant DNA techniques.

Dysentery (shigellosis), caused by several serotypes of the Shigella species, is a serious endemic diarrheal disease among infants and has produced serious epidemics in Eastern India in recent years. With the most lethal form of shigellosis, dehydration is not a problem, and thus oral rehydration therapy is ineffective in over 90% of cases. Antibiotics are required for therapy, and early accurate diagnosis is essential for the antibiotics to be effective. A significant portion of ongoing shigellosis research is directed toward development of efficient rapid immunodiagnostic techniques. Other research in this area is focused on development of recombinant oral attenuated vaccines which may be directed toward Shigella species only or a combination of Shigella and other enteric pathogens such as typhoid or enterotoxigenic E. coli, the cause of travelers' diarrhea. Research on diagnostic techniques and vaccines for dysentery will be eligible for research awards.

Rotavirus is the most common cause of diarrhea in infants, and is the most common cause of death among the diarrheal diseases in this most vulnerable age-group. Immunization offers the only prospect for prevention of this disease, and several vaccine prototypes have been developed, including a rhesus rotavirus vaccine developed at NIH and a less attenuated bovine vaccine developed at the Wistar Institute. Field trials and other research related to rotavirus vaccines will be eligible under the project.

Hepatitis, both hepatitis B and non-A, non-E forms of the disease, are judged to be serious enough and to offer sufficiently optimistic opportunities for control with vaccines to warrant eligibility under the project although the morbidity and mortality statis-

tics are not as striking as other diseases which can be prevented through immunization. The development of a second generation of hepatitis B vaccines which are vectored in mammalian, yeast and, possibly, vaccinia virus offers prospects for affordable, high-level protection.

Rabies, fortunately, does not figure prominently in the morbidity and mortality statistics in India, but this dreaded, uniformly fatal disease is common enough to cause millions of Indians to seek expensive, risky post-exposure immunoprophylaxis. While the relative burden of disease caused by rabies is not high, the opportunity to apply modern biotechnology effectively in the development of an oral vaccine to control the disease in the canine reservoir generates considerable enthusiasm among both Indian and U.S. scientists and public health officials. Recent advances in development of oral rabies vaccines through the application of recombinant DNA technology and vaccinia virus vectors and the canine baits which will be used to distribute the vaccine will be extended in Indian institutions through collaborative research projects.

Pertussis (whooping cough) ranks second only to measles as a cause of serious morbidity and mortality which can be prevented by immunization. However, the whole cell vaccines in current use cause side effects that limit their acceptability throughout the world including India and the U.S. The Government of India is committed to adopting acellular pertussis vaccine manufacturing techniques. Eligible for support under the project will be collaborative research and research training for scientists who will develop and manufacture the Indian acellular vaccine. Also, field tests in India of acellular pertussis vaccines, which have been developed and are currently under trial in Western Europe, will be eligible.

Pneumococcal pneumonia is the most common cause of acute respiratory infection (ARI) mortality in children in India and throughout the world. Both the existing 23-valent unconjugated S. Pneumoniae polysaccharide vaccine and new protein-polysaccharide conjugate vaccines which are under development will be eligible for research support under the program. These vaccines were identified unequivocally as the highest priority in the U.S. National Academy of Sciences/Institute of Medicine recent report of priorities for vaccine development in international (developing country) settings.

Malaria is not a major killer in India although there are two million cases of the disease reported annually. However, a shift in the distribution of the type of malaria toward the more virulent P. falciparum and wider distribution of the strains resistant to inexpensive therapeutic measures suggest the fatality-case ratio may increase. The development of an effective primary prevention measure such as a vaccine has long been a goal of biomedical research. The advent of biotechnology has substantially raised the chances of suc-

cessfully developing a malaria vaccine and, indeed, several investigators have announced technological breakthroughs in recent years. Progress has also been made in the development of diagnostic techniques. In fact, there is, at present, an Indian study underway for a malaria diagnostic test that seeks to bypass dependence on the microscope for diagnosis. Research to develop vaccines against different stages and species of the malaria parasite and to develop diagnostic techniques will be eligible for support under this component. This research will not duplicate the basic research on the immunology of malaria sponsored as part of the Gandhi - Reagan Science and Technology Initiative, begun in 1982.

2. Project Component Two: Malaria Field Trials

Over the past twenty years, AID has invested more than \$45 million to support 43 malaria research projects around the world. As a result of its investment, AID was able to announce in August 1984 [a breakthrough that has major implications for the eradication of malaria - the development of a synthetic peptide vaccine against the most deadly form of human malaria, P. falciparum. In May 1986, initial Phase I human safety trials of the synthetic P. falciparum vaccine were begun on U.S. volunteers at the Vaccine Development Center at the University of Maryland. If all goes as expected, the Phase II human trials to determine immunogenicity of the vaccine will be underway in the U.S. by January 1987. Phase III safety and efficacy trials in populations in which malaria is encountered are scheduled to begin soon after the results of the Phase II trials are known. The Phase III trials will be conducted under field conditions permitting natural mosquito challenge.

The Phase III trials are being sponsored under an AID Science and Technology Bureau project, Malaria Immunity and Vaccination Research. The AID S&T Bureau is currently in the process of selecting those countries in which the Phase III trials will take place. India is a prime candidate for the Phase III trials both because of the high incidence of malaria in the country -- approximately two million reported cases per year, with a large proportion of P. falciparum -- and because of the highly trained scientists and technicians available to participate in the field trials. The S&T Bureau estimates that \$5 million will be required over a five year period to conduct the Phase III trials in India. USAID/India proposes to contribute \$1 million to the effort through this project provided that India is one of the countries selected to take part in the field trials. The remaining \$4 million will be provided by the S&T Bureau.

Assuming the Phase III trials are successful, a vaccine for P. falciparum malaria could be commercially available as early as 1992.

3. Project Component Three: Center for Epidemiological Research and Training

To conduct field research on diseases and corresponding vaccines, it is useful to have access to a well-defined population for which intensive health profile and demographic information is available. This approach has proved useful for the International Centre for Diarrhoeal Disease Research, Bangladesh, and two epidemiological research centers in Egypt for which the U.S. Centers for Disease Control is a collaborating institution.

India intends to establish a Center for Epidemiological Research and Training (CERT) at the Tuberculosis Research Center at Trivullore, a laboratory under the jurisdiction of the Indian Council of Medical Research. Sanctions and budgets for the CERT are already in place. The CERT will develop a core epidemiological data base within a defined population and the capability to field test appropriate vaccines and diagnostic techniques with the cooperation of this defined population. The CERT will, in addition, develop a mobile epidemiological support capability to backstop field research in other parts of India.

CDC will be the principal U.S. collaborating institution and the U.S. Public Health Service has set aside the rupee equivalent of \$930,000 to support the collaboration. A copy of the CERT-CDC proposal which defines the specific objectives and methodology of the collaboration is attached at Annex-5 to this Project Paper.

USAID, through this project, will contribute \$250,000 to cover the foreign exchange requirements of the CERT-CDC collaboration. These funds will be used primarily to upgrade CERT computer and laboratory facilities and to provide opportunities for CERT staff to travel to the U.S. to collaborate with American counterparts.

D. Project Inputs/Outputs

1. Inputs

- Research support through grants, amendments to research contracts and other awards to Indian and U.S. collaborating scientists. (Research support includes allowances for collaborative visits, equipment and supplies, technical staff, clinical tests, communications, and publications.)
- Technology transfer to Indian scientists and technologists of current techniques in research methodology, disease surveillance, and quality control of vaccine manufacture.

2. Outputs

- New and improved vaccines to extend the range of diseases which can be prevented through immunization.
- New and improved immunodiagnostic technologies to improve the efficacy of patient care and to make seroepidemiologic surveys of vaccine-preventable diseases feasible so public health planners can develop effective disease control strategies.
- Indian scientists and technologists familiarized with the most current research and epidemiological methodologies that are germane to vaccine and immunodiagnostic development, disease surveillance, and quality of vaccine manufacture.

IV. Project Implementation

A. The Vaccine Action Program and its Administrative Infrastructure

In April 1985 the Seventh Session of the Indo-U.S. Sub-commission on Science and Technology recommended the development of new and improved vaccines as a priority for Indo-U.S. cooperation. This recommendation reflected the widely recognized potential benefits of vaccine research; the highly regarded capabilities of the Indian and U.S. scientific communities; and the historical success of Indo-U.S. research collaboration in the health sciences.

Following up on the recommendation of the Subcommittee, in June 1985, President Reagan and Prime Minister Gandhi announced the initiation of a new program to bring together U.S. and Indian scientists to jointly develop and test new and improved vaccine for immunization against diseases in India and to focus on vaccine production, quality control, and immunization delivery methodology. This new effort was designated the Indo-U.S. Vaccine Action Program (VAP).

A Memorandum of Understanding (MOU) between the two governments for the implementation of VAP was drawn up in November of 1985 and is currently moving through the clearance channels in both countries. As the MOU indicates, the VAP will involve the Department of Biotechnology, the Ministry of Health and Family Welfare, and the Indian Council of Medical Research on the Indian side and AID and the U.S. Public Health Service on the American side. A copy of the MOU is provided in Annex-6.

The VIDX Project is the channel through which AID resources will be routed to support the research, malaria field trials, and CERT components of the VAP. To execute the VIDX Project, AID will

rely, to some extent, on the administrative infrastructure set up under the VAP. Consequently, it is useful for the reader to understand the VAP infrastructure.

1. The Joint Working Group

A Joint Working Group (JWG) composed of equal numbers of Indian and American scientists and senior administrators will be organized under the VAP. The VIDX project will rely on the JWG to approve disease areas identified for priority attention and to provide policy and procedural guidance. JWG responsibilities under the VAP include:

review program plans and recommend new areas of cooperation, based on recommendations from technical workshops and collaborating scientists;

recommend measures to both Governments to assure that the Program operates smoothly;

address issues requiring joint resolution;

ensure that efforts under the VAP do not conflict with or duplicate any other Indo-U.S. scientific collaboration;

establish and communicate guidelines and criteria for selection of projects for inclusion in the VAP.

The JWG will meet in connection with the periodic Indo-U.S. Science and Technology Subcommittee meetings or at such other times as may be deemed necessary by both Governments.

The Indian side of the JWG is most likely to include the Secretary, Department of Biotechnology (chair); the Director-General of the Indian Council of Medical Research; the Director-General for Health Services, Ministry of Health and Family Welfare; a representative from the Office of the Drug Controller, GOI; a representative of the Planning Commission; and a representative of the Medical Academies.

The U.S. side of the JWG is most likely to include the Senior Assistant Administrator, Bureau for Science and Technology, AID (chair); the Director, USAID/India; the Surgeon General of the U.S. Public Health Service; the Associate Director for International Research, National Institutes of Health; the Director of the Microbiology and Infectious Diseases Program, National Institute of Allergy and Infectious Diseases; a representative of the Centers for Disease Control; and a representative of the Institute of Medicine/National Academy of Sciences.

2. The Executive Agency/Secretariat

In order to ensure that the VAP operates smoothly between Joint Working Group meetings and to help sustain the collegial nature of the program, each side will designate an Executive Agency/ Secretariat. On the Indian side this will be the Department of Biotechnology. U.S. responsibilities will be handled by the Public Health Service, Office of International Health. The responsibilities of the respective Executive Agencies/Secretariats are described below. The last three of these are particularly relevant to the VIDX Project.

Be responsive to the Joint Working Group in assuring that the VAP operates as directed by the policies and guidelines set forth by the Joint Working Group;

Take necessary and appropriate actions, in cooperation with other participating agencies on their respective sides, to facilitate the implementation of the VAP;

Collect information (such as evaluations and progress reports prepared in connection with specific activities) in order to assist the Joint Working Group with its responsibility of assessing progress of the VAP and in preparation of the annual report on VAP;

Serve as a clearinghouse for ideas and recommendation for activities/projects under the VAP, assuring that these are presented to appropriate authorities and the VAP program leadership;

Maintain an information network in order to keep other parties engaged in scientific cooperation with India informed and to assure that there is no conflict or duplication with other Indo-U.S. collaborative activities, including the Gandhi-Reagan Science and Technology Initiative, begun in 1982.

3. Technical Coordinator

Technical Coordinators will be appointed by both the Indian and U.S. Governments. The Indian Technical Coordinator will be the designated by the Secretary, Department of Biotechnology. The American Technical Coordinator will be the Senior Medical Science Advisor to the Director, Fogarty International Center. (The Fogarty International Center is an organization of the National Institutes of Health, a part of the U.S. Public Health Service.) The Technical Coordinators' primary responsibilities will be directed toward the VIDX project, although they may also assist the executive agency/secretariat in the discharge of its information collection and dissemination responsibilities for other activities under VAP.

For the research awards component and the malaria field trials components of the VIDX project, the Technical Coordinators will arrange for technical and ethical reviews of protocols, coordinate technical communications among scientists, organize scientific meetings, and provide information to collaborating scientists on training opportunities and technical programs.

B. Implementation of the Research Awards Program

1. Institutional Arrangements for the Research Awards Program

For the Research Awards Program -- the central component of the VIDX -- the implementing agency on the Indian side will be the Department of Biotechnology. The implementing agency on the American side will be the U.S. Public Health Service. The implementing agencies will be responsible for coordinating the joint effort, promoting the project among respected scientists and laboratories, managing the protocol review process, making the research awards, and ensuring the quality of science sponsored under the project. Both implementing agencies will, for the purposes of this project, operate under the guidance of the Joint Working Group established under VAP.

As indicated in the previous section, the Department of Biotechnology will act as the executive agency/secretariat for the Vaccine Action Program and for the VIDX project. To manage the technical aspects of the VIDX project, DBT will coordinate closely with the Indian Council of Medical Research.

Within the Public Health Service, the Office of International Health will act as the executive agency/secretariat. The Fogarty International Center, also part of the PHS, will manage the technical aspects of VIDX. AID will finance the Public Health Services involvement through a Participating Agency Services Agreement.

2. Protocol Preparation and Review Process for the Research Awards Program

Research protocols will be developed jointly by Indian and American scientists interested in receiving support under the project. Several collaborative concepts have already been formulated as a result of meetings held March 31 - April 2, 1986 at NIH. Additional collaborative concepts within the mutually accepted priority areas are expected from leading scientists who could not attend the meetings but who have expressed interest in the program.

The protocol format to be followed will satisfy the requirements of both the Indian and the American biomedical research application process, and will be modified to accommodate: a) an explanation of the relevance of the proposed research to the goals of the Indo-U.S. Vaccine Action Program, b) a clear expression of the

responsibilities of the Indian and the American collaborators throughout the proposed study, and c) a budget that illustrates how the rupee and the dollar expenditures will be coordinated to achieve the proposed research goals.

Upon completion, identical research protocols will be presented simultaneously to the Department of Biotechnology and to the Fogarty International Center of the U.S. Public Health Service. These institutions will secure administrative, ethical, and technical reviews. The review process will be developed by the Department of Biotechnology and the Public Health Service once the project commences. Following is an illustrative example of how the process is likely to work.

a. Administrative Review: Protocols will first be reviewed to ensure that the participating scientists have approval of their respective institutions to accept and administer any awards made in accordance with the regulations governing VIDX. At the same time protocols will be reviewed to confirm that they are germane to development or testing of vaccines or immunodiagnostic technologies in priority areas of the project.

On the Indian side this review will be coordinated by the Department of Biotechnology. On the American side this review will be the responsibility of the Fogarty International Center. Once the suitability of the protocol has been established by both sides and any differences of opinion have been settled through negotiation with the principal investigators, the protocol will be submitted for ethical and technical review.

b. Ethical and Technical Review: Protocols that conform to VIDX objectives will be submitted for ethical review of research involving humans as experimental subjects (if appropriate) and for technical peer review. The ethical and technical reviews will be managed by the respective Technical Coordinators.

The process of insuring adequate ethical review of protocols, which has been negotiated by the Indian and U.S. governments, is outlined in the MOU contained in Annex VI. Once the ethicality of a protocol has been assured, the protocol will be submitted for technical peer review.

To obtain technical peer review of protocols, the respective Technical Coordinators will submit copies of the protocols to experts who are knowledgeable about current research directions and about the research technology to be applied in the protocol. The experts will independently review the protocol for technical feasibility, competence of investigators, and research environment of the participating laboratories. They will provide written comments that will form the basis of a summary of the review to be prepared by

the Technical Coordinators. These summaries will categorize the comments of reviewers into: suggestions, which the principal co-investigators may accept; and recommendations, which will require a specific response from the co-investigators.

After the protocol has been accepted on administrative, ethical and technical grounds, the respective Technical Coordinators will communicate the results of their independent reviews with the co-investigators and with each other, and they will attempt to negotiate any differences which may have arisen during the review.

3. Project Implementation Responsibilities for the Research Awards Program

a. Collaborative Visits

The greatest amount of project resources will support the travel of Indian scientists and technologists to the U.S. and of American scientists and technologists to India. These short term visits will permit participants to share information, collaborate on specific research problems, and, in general, further the progress of research being conducted. Collaborative visits will also be used to familiarize Indian scientists and technicians with the most current research and epidemiological methodologies that are germane to vaccine and immunodiagnostic development, disease surveillance and quality control of vaccine manufacture. This latter category of collaborative visit could be short or long term.

Funds required for the costs of the collaborative visits will pass from AID through the PASA with the Public Health Service to the participants or, as appropriate, to the host laboratory. The American Embassy Science Office in New Delhi, through its Public Health Service Officer and his staff, will assist with international travel arrangements for participating Indian scientists and technicians.

b. Commodity Procurement

Equipment and supplies for both Indian and American scientists will be financed through VIDX; however, the majority of equipment and supplies will be for Indian scientists. Equipment and supplies procured for U.S. scientists will be the responsibility of the U.S. scientist and his laboratory. Equipment and supplies procured in India for Indian scientists will be the responsibility of the benefiting scientist and laboratory. Procurement of U.S. equipment and supplies for Indian scientists will be done by the American counterpart scientist and his laboratory at the request of the Indian scientist. The benefiting Indian scientist will be responsible for obtaining the required Not Manufactured in India Certificate, for ensuring that GOI taxes on the procurement are paid from a non-U.S.

government source, and for transportation of the commodities from the port of entry to the benefiting laboratory.

All procurements financed by AID will be done so in accordance with AID rules and regulations governing procurement.

4. Illustrative Project Implementation Schedule for Research Awards Program

- April 1986 - Indian and American scientists meet at NIH to select priority disease areas and to begin preparation of protocols.
- July 1986 - Project Agreement for VIDX signed between Indian and American Governments.
- July 1986 - Memorandum of Understanding signed for VAP between Indian and American Governments.
- Oct. 1986 - Joint Working Group meets to approve priority disease areas recommended by Indian and U.S. scientists and to establish VAP policies and procedures.
- Nov. 1986 - Submission of research protocols begins.
- Feb. 1987 - First batch of protocols completes review process and collaborative research activities commence.
- Dec. 1988 - Mid-term evaluation of VIDX project.
- July 1992 - Project Assistance Completion Date.

C. Implementation of the Malaria Field Trials

1. Institutional Arrangements for the Malaria Field Trials

This component of the project will be managed by AID/Washington's Science & Technology Bureau through contracts that have already been let under its Malaria Immunity and Vaccination Research Project. The American institutions that have been selected to participate are the University of Maryland and the American Institute of Biological Sciences. The Indian counterpart is the Malaria Research Centre, Delhi. These institutions will be responsible for selecting appropriate sites, jointly formulating the research protocol, and coordinating all activities that relate to the conduct of the research trials.

2. Protocol Preparation and Review Process for the Malaria Field Trials

Indo-U.S. collaboration on the malaria field trials will begin with the identification of specific sites and the joint formulation of a research protocol. This protocol will be subjected to the review process set up for the Research Awards Program (described above). In addition to a plan for the actual field trials, the protocol will incorporate a plan for an epidemiological data gathering exercise that will take place prior to the field trials. Epidemiological data is necessary to acquire an accurate profile of the target population so that the results of the trials can be interpreted properly. The data gathering exercise will take 18-24 months to complete. The trials will follow the development of the target population health profile and will take 24-36 months.

3. Project Implementation Responsibilities for the Malaria Field Trials

Commodity procurement, collaborative visits, and technical services requirements will be identified in the research protocol jointly developed by the Indian and American collaborators. Arrangements for providing those inputs financed with AID dollars will be the responsibility of the AID/Washington Science & Technology Bureau. The S&T Bureau will rely on the contracts that have been let under the Malaria Immunity and Vaccination Research Project to arrange for provision of the inputs. The USAID/India Training Office will assist with international travel arrangement for participating Indian scientists.

4. Illustrative Project Implementation Schedule for the Malaria Field Trials

- May 1986 - Phase I human safety trials begin at University of Maryland.
- Aug. 1986 - Indian and American collaborators begin to develop protocol for India field trials.
- Jan. 1987 - Phase II immunogenicity trials begin at University of Maryland.
- Jan. 1987 - Protocol for India field trial submitted for review to the Indian Department of Biotechnology and to the U.S. Public Health Service.
- Mar. 1987 - Protocol approved.
- Apr. 1987 - Epidemiological data gathering exercise begins.

- Dec. 1988 - Mid-term evaluation of VIDX project.
- Apr. 1989 - Epidemiological data gathering exercise concludes.
- May 1989 - Field trials commence.
- May 1992 - Field trials conclude.
- July 1992 - Project Assistance Completion Date.

D. Implementation of Center for Epidemiological Research and Training (CERT) Component

1. Institutional Arrangements for CERT

The creation of CERT will be directed by the Indian Council of Medical Research (ICMR) through the Tuberculosis Research Center at Trivullore. The U.S. Centers for Disease Control (CDC) will assist the ICMR. The Public Health Service has set aside the rupee equivalent of \$930,000 for the CDC and the ICMR to draw upon for the CERT activity. AID will contribute \$250,000 through a PASA with the CDC.

2. Project Implementation Responsibilities for CERT

Commodity procurement, collaborative visits, and technical services requirements will be jointly identified by CERT and CDC. Arrangements for providing those inputs financed with AID dollars will be the responsibility of CDC. The Embassy Science Office, through its Public Health Service Officer and his staff, will assist with international travel arrangements for participating Indian scientists.

3. Project Implementation Schedule for CERT

A detailed proposal and timetable for implementation will be jointly developed by CERT and CDC during the summer of 1986. The timetable will track against the following general objectives of the CERT/CDC collaboration which have already been negotiated:

identify the elements necessary to establish a center for epidemiological research and training;

identify a stable, well-defined population or populations in which epidemiological studies can be carried out;

examine the available baseline demographic data and assess the currently available epidemiologic information on diseases which can be prevented by currently available vaccines or which may be prevented by new vaccines;

identify and/or train the personnel necessary for more detailed collection of epidemiologic data on diseases currently preventable by immunization or subject to being prevented with technologic advances;

carry out selected studies needed to accurately delineate the characteristics of polio, measles, tetanus, diphtheria and pertussis in the defined population;

evaluate the effectiveness of vaccines and vaccination programs in current use in the defined population;

assist in the necessary studies, including the evaluation of new diagnostic tests, to accurately delineate the epidemiology of other diseases against which newly developed vaccines could be used effectively;

assess the safety and efficacy of any newly developed vaccines which may be adopted for future use. Likely candidates include vaccines against invasive Hemophilus influenzae disease, hepatitis A and B, influenza, malaria, meningococcal disease, pertussis, respiratory syncytial virus, rotavirus, and bacterial enteric pathogens;

make available any information collected for possible use in developing or modifying vaccination policies or in vaccine delivery.

E. USAID Management Responsibilities

In USAID/India project management responsibilities will rest with the Office of Health and Nutrition. Given the active participation of the Embassy Science Office, the PHS and the AID S&T Bureau, USAID does not anticipate that any additional staff will be required to manage the project.

V. Monitoring and Evaluation

A. Monitoring

The project will be monitored on several different levels. The overall progress of the VIDX project will be monitored by the VAP Joint Working Group. Annual reports on project status will be prepared by the Executive Agencies/Secretariats for submission to the JWG. The reports will list and describe the active sub-projects and identify problems that require JWG attention.

Specific sub-projects will be monitored by the implementing agencies, i.e., the Department of Biotechnology in India and the U.S. Public Health Service (the Fogarty International Center for the research awards program and the CDC for the CERT) and the AID S&T Bureau (for the malaria field trials) in the U.S. Small sub-projects will be monitored by scientists appointed by the implementing agencies

whereas large sub-projects will be monitored by specially appointed technical committees. Monitoring will ensure the quality of the research being conducted as well as adherence to VAP policies and procedures.

Representatives from USAID/India and the Department of Biotechnology will periodically visit sub-project sites to obtain feedback on the program from participating investigators and to ensure that no U.S. Government or Government of India policies are being violated.

B. Evaluation

The project will be subject to evaluations commissioned by the JWG as part of an overall evaluation of the Vaccine Action Program and to AID mid-term project and end-of-term AID evaluations. The evaluations will seek to determine:

- the quality and relevance of research being sponsored;
- the performance of sub-projects in relation to agreed upon protocols and research objectives;
- the effectiveness and appropriateness of VAP policies and procedures;
- the impact and potential impact of the project on health sector strategy goals; and,
- U.S. and Indian Government performance in managing the project.

VI. Project Analyses

A. Technical Analysis

Disease areas that will be eligible for research support under the project were identified jointly by Indian and American scientists based on the seriousness of the threat posed by the disease to the Indian population, the potential for near term success in developing a vaccine or diagnostic technique, and the level of interest in the disease areas on the part of Indian and American scientists. Brief technical descriptions of the research opportunities in each of the disease areas selected for attention can be found in Section III of this Project Paper entitled "Project Description."

Thorough technical reviews of protocols submitted under the Research Awards Program and the Malaria Field Trials components of the project will be conducted in accordance with the process described in Section IV of this project paper entitled "Project Implementation."

B. Institutional Analysis

1. Public Sector

Indian medical research institutions are among the most vigorous in the Indian research establishment. This is reflected by the quality of science conducted at the institutions and the international recognition granted to that science. Of the four Indian scientific publications which were cited in the international technical literature fifty or more times (an arbitrary criterion in judging "significant impact"), all were in the biomedical or biological field.

A overview of the Department of Biotechnology (the implementing agency for this project) and its priorities for biomedical research can be found in Section II of this paper entitled "Background and Project Rationale." The Department of Biotechnology has a good cooperative relationship with the Indian Council of Medical Research, the lead government agency in the promotion of biomedical research. The ICMR is a semi-autonomous GOI organization that falls under the Ministry of Health and Family Welfare. It operates national laboratories that focus research on specific health problems, such as the National Institute of Cholera and Enteric Diseases in Calcutta, the National Institute of Virology in Pune, and the Tuberculosis Research Center at Trivullore.

The Ministry of Health and Family Welfare also oversees other organizations that engage in biomedical research. The Malaria Research Centre is an institution of the MOHFW. The Pasteur Institute at Coonoor and the Central Research Institute at Kasauli are institutions of the MOHFW that have responsibility for production as well as research. The Pasteur Institute is doing work on diphtheria, tetanus, pertussis, and rabies while the Central Research Institute is concerned with diphtheria, tetanus, pertussis, rabies, cholera, and typhoid.

The Council for Scientific and Industrial Research network supports biomedical research at a few of its labs. The primary laboratory for biomedical sciences in the extensive CSIR network is the Central Drug Research Institute (CDRI) in Lucknow where a large staff is engaged in biomedical research using the latest biotechnical techniques. CDRI is known particularly for its work in cholera and amoebiasis. The CSIR mandate is to produce technology applicable to the commercial and industrial sector, and within this context the CDRI research is aimed primarily at new drug development with considerable effort also going toward development of rapid diagnostic tests and basic microbiological research.

Several universities are active in biomedical research. Faculty at the All-India Institute of Medical Sciences (AIIMS), the

Banaras Hindu University, the Jawaharlal Nehru University, and the Christian Medical College in Vellore, all premier research institutions, have established collaborative links with U.S. colleagues. Their research has been supported through India's University Grants Commission as well as through the Department of Biotechnology, the ICMR and other sources.

2. Private Sector

In the private sector, non-profit foundations such as the Tata Institute for Fundamental Research represent a considerable resource for biotechnology research. The bulk of support for the conduct of research at this institute and other foundations comes from public sources for which institute scientists compete successfully. The quality of research is adequate for some of the staff to compete successfully for research funds from the U.S.

In the industrial or commercial segment of the private sector there is evidence of sporadic, "as needed" biotechnical research. As expected, the research is very directed. The small entrepreneur does not yet exist in the biotechnology field in India. According to Indian scientists, several firms have been approached to solicit interest in developing a commercially viable biotechnology industry, but none has yet expressed interest.

C. Economic Analysis

Investments in the health sector are economical because of the obvious gains in productivity realized by the availability of a vigorous workforce. Moreover, the economic value of preventive versus curative health care measures is widely recognized.

Judged against the cost of other preventive measures, such as altering environmental conditions, vaccines consistently prove to be among the most cost-effective. This is amply demonstrated in the case of malaria. The Government of India estimates that approximately \$150 million a year is spent in the control of malaria, primarily for the procurement of malathion. The newly developed malaria vaccine which is expected to be commercially available by 1992 will cost less than fifty cents per dose. At two doses per 18 million children a year (the GOI target), the annual cost of national protection is estimated at less than \$18 million. Even with delivery costs figured in, the savings will be substantial.

Vaccines are even more economical because of the synergism that exists between diseases. For example, it is generally accepted that measles and diarrhea have an interactive relationship, with the presence of measles promoting the morbidity and mortality of infectious diarrheal diseases. It is also suspected that there is a direct relationship between the presence of viral and bacterial respiratory infections. Consequently, a vaccine for one disease may

in practice avert a disease incidence greater than that nominally attributed to the disease against which the vaccine is directed.

This project will be particularly conscious of cost-effectiveness. It will support only research that promises near-term results or research that has the potential to affect diseases that have been identified as major contributors to India's high infant morbidity and mortality rates. It will also seek to reduce the burden and thus the cost of vaccine delivery by limiting the number of doses required or by combining different vaccines in one dose.

D. Social Soundness Analysis

This is a vaccine research project for which a social soundness analysis is not as critical or as appropriate as it would be if this were a vaccine delivery project. There are, however, several points should be emphasized.

Vaccines are among the most socially acceptable of the known methods of disease prevention. This project will increase the acceptance of vaccines by sponsoring research that lessens the incidence of adverse reactions and heightens the efficacy of vaccines. The acceptance of vaccines will be further promoted through the communications component of the Child Survival Support Project.

Although the rural poor, particularly children under five years of age, are the targeted beneficiaries of this project, they will not be involved in its implementation except when epidemiological field studies or vaccine research trials are underway. During these instances, care will be taken to ensure that the approaches used to gather information or dispense vaccines are approaches that do not conflict with local customs. Moreover, any research activity involving human subjects will be subject to continuing review boards set up in the respective countries to protect the rights and welfare of participating human subjects. Annex 1 of the MOU for the VAP requires that before human subjects are involved in research, proper consideration will be given to the risks to the subject; the anticipated benefits to the subjects and others; and the importance of the knowledge that may be reasonably be expected to result. No human subject will be involved without his/her informed consent.

E. Environmental Analysis

It is not anticipated that this project will have any negative environmental impact. The Asia Near East Bureau environmental coordinator has confirmed that the project is subject to the "categorical exclusion" permitted under provision 22CFR216 of the "AID Environmental Procedures". In the event, however, that an activity is identified that could have a negative environmental impact, both sides will strictly observe the applicable environmental regulatory requirements.

Needless to say, care will be taken to ensure the proper storage and disposal of vaccines, chemical and other materials to be used in the program.

VII. Financial Plan

A. Disbursements

Disbursements for this Project will flow through five streams: 1) a PASA with PHS, 2) a PASA with CDC, 3) a buy-in to the S&T Bureau project for Malaria Immunity and Vaccination Research, 4) direct GOI expenditures, and 5) direct AID expenditures.

The PASA with PHS will be signed upon receipt of written GOI approval. The purpose of the PASA will be to provide assistance to the research awards program described in component one of the project. Eligible costs under the PASA, which will be limited to costs incurred through collaboration, will include collaborative travel, training for Indian scientists, supplies and equipment, and research support costs. Disbursements will be made on a cost-reimbursable basis by the USAID/India Controller after expenditure statements from PHS have been received and administratively approved by the USAID/India Office of Health and Nutrition. The expenditure statements prepared by PHS will indicate, by expenditure categories, cumulative expenditures and expenditures made during the period for which reimbursement is sought.

The PASA with CDC will be signed upon receipt of written GOI approval. The purpose of the PASA will be to provide assistance to the Centre for Epidemiological Research and Training described in component two of the project paper. Eligible costs under the PASA will include collaborative travel for Indian scientists, and equipment and supplies for the CERT. Disbursements will be made on a cost reimbursable basis by the USAID/India controller after expenditure statements from CDC have been received and administratively approved by the USAID/India Office of Health and Nutrition. The expenditure statements prepared by CDC will indicate, by expenditure categories, cumulative expenditures and expenditures made during the period for which reimbursement is sought.

The buy-in to the S&T Bureau project, Malaria Immunity and Vaccination Research, will also have written GOI approval. Once that approval is received, fund cites will be cabled to the S&T Bureau, and funds will be added to existing contracts under the S&T project. Disbursement will be made by AID/Washington after expenditure statements have been administratively approved by the S&T Project Manager.

The Government of India will claim reimbursement for costs it incurs under the Project in accordance with the standard procedures adopted by USAID/India and the GOI for these transactions. Government of India costs are expected to include research support and locally procured equipment.

Funds for the travel of Indian collaborators will be expended directly by AID either through the USAID/India Training Office or through the Embassy Science Office. Other cost for which AID might be asked to make a direct expenditures include foreign exchange financed equipment and supplies although, for the most part, these procurements will be done by the collaborating U.S. institutions and financed through the PHS and CDC PASAs.

B. Budget

This is a research project. Exact project inputs and the cost of inputs will not be known until research proposals have been submitted and approved. Cost categories shown below accurately reflect items on which funds will be spent, but the numbers within the cost categories are notional.

VACCINE AND IMMUNODIAGNOSTIC DEVELOPMENT PROJECT

ILLUSTRATIVE BUDGET FOR LIFE OF THE PROJECT**

(In Thousands of Dollars)

C A T E G O R Y	AMOUNTS AND SOURCES OF FUNDING				PROJECT TOTAL
	AID	S&T AID	U.S. Public Health Service*	Government of India*	
<u>I. Research Awards</u>					
<u>A. Collaborative Scientific Visits/Short Term</u>					
<u>Indian Scientists to U.S.</u>					
Travel	25		300		325
Per Diem and Other Costs	876				876
<u>U.S. Scientists to India</u>					
Travel	-		200		200
Per Diem	-		145		145
Miscellaneous	29				29
Subtotal for Collaborative Scientific Visits/Short Term	930	-	645	-	1,575
<u>B. Collaborative Indian Scientific Visits to U.S./Long Term</u>					
Per Diem and Other Costs	420	-	-	-	420
Travel	8	-	30	-	38
Miscellaneous	67	-	-	-	67
Subtotal for Collaborative Scientific Visits/Long Term	495	-	30	-	525
<u>C. Equipment</u>	1,709	-	-	300	2,009
<u>D. Supplies</u>	500	-	-	500	1,000
<u>E. Research Support</u>					
Salaries of Scientists				1,000	1,000
Salaries of Research Support Personnel (Technical)	500	-	-	-	500
In-India Travel	-	-	-	200	200
Clinical Laboratory Tests	250	-	-	-	250
Communications and Publications	100	-	-	-	100
Field Trial Costs other than Supplies, Equipment, and Personnel	200	-	-	-	200
Subtotal for Research Support	1,050	-	-	1,200	2,250
<u>TOTAL FOR RESEARCH AWARDS</u>	4,684	-	675	2,000	7,359

* Rupee equivalent converted at \$1 = Rs.12.50.

** Subject to the availability of funds

CONTINUATION OF ILLUSTRATIVE BUDGET**
(In Thousands of Dollars)

C A T E G O R Y	AMOUNTS AND SOURCE OF FUNDING				PROJECT TOTAL
	AIDD	S&T AID	U.S. Public Health Service*	Government of India*	
<u>II. Center for Epidemiological Research & Training (CERT)</u>					
A. Collaborative Visits of Indian Scientists to the U.S.	91	-	34	-	125
B. Collaborative Visits of U.S. Scientists to India	-	-	112	-	112
C. Equipment	125	-	-	-	125
D. Data Collection/Field Trials	-	-	800	-	800
E. CERT Operating Expenses	-	-	-	5,000	5,000
<u>TOTAL FOR CERT</u>	216	-	946	5,000	6,162
<u>III. Malaria Field Trials</u>					
A. Research Technical Personnel (U.S. and Indian)	500	3,000	-	-	3,500
B. Supplies & Equipment	350	850	-	-	1,200
C. Clinical Laboratory Tests	75	75	-	-	150
D. Communications & Publications	75	75	-	-	150
<u>TOTAL FOR MALARIA FIELD TRIALS</u>	1,000	4,000	-	-	5,000
IV. Project Evaluation	100	-	-	-	100
<u>PROJECT TOTAL</u>	6,000	4,000	1,621	7,000	18,621

* Rupee equivalent converted at \$1 = Rs.12.50.
** Subject to the availability of funds

VIII. Conditions Precedent to Disbursement

A. Conditions Precedent

Prior to the disbursement of any funds for bench, clinical, or field research, the Cooperating Country will provide, or cause to be provided evidence that:

1. the Memorandum of Understanding between the Government of India and the Government of the United States for the implementation of the Vaccine Action Program has been signed; and
2. the first session of the Joint Working Group has been held and has identified priority disease areas for Indo-U.S. collaboration and has developed and approved overall policies and procedures for the Vaccine Action Program.

B. Covenants

1. In the event that an activity is identified that has the potential for a negative environmental impact, both sides will strictly observe the applicable environmental regulatory requirements.
2. AID and the Department of Biotechnology agree to establish an evaluation program as part of the project. Except as AID and the Department of Biotechnology otherwise agree in writing, the program will include, during the implementation of the project and at one or more points thereafter:
 - (a) evaluation of progress toward attainment of the objectives of the Project;
 - (b) identification and evaluation of problem areas or constraints which may inhibit such attainment;
 - (c) assessment of how such information may be used to help overcome such problems; and
 - (d) evaluation, to the degree feasible, of the overall development impact of project.

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ANNEX-I

LOGFRAME

VACCINE AND IMMUNODIAGNOSTIC DEVELOPMENT
LOGICAL FRAMEWORK

	Verifiable Indicators	Important Assumptions
<p><u>Sector Goal:</u></p> <p>To reduce mortality and morbidity among children and infants and individuals in the labor force.</p>	<p>Reduction in the infant mortality rate from 105 to 60 by the year 2000.</p> <p>Fall in death rate from 15 to 9 by the year 2000.</p>	<p>The availability of improved vaccines and diagnostic technologies can have a significant impact on mortality and morbidity rates.</p>
<p><u>Project Purpose:</u></p> <p>To develop vaccines and improved diagnostic techniques for use in the Indian health care system.</p>	<p>New or improved vaccines and diagnostic techniques will be further along in the technology development pipeline.</p>	<p>The advent of biotechnology has created a potential for vaccine and diagnostic technique development that didn't exist six years ago.</p> <p>Indian and American scientists are capable of collaborating successfully.</p>
<p><u>Outputs:</u></p> <p>New and improved vaccines:</p> <p>New and improved immuno-diagnostic techniques:</p> <p>Indian scientists and technologists familiarized with the most current research and epidemiological methodologies.</p>	<p>Selected vaccines and diagnostic techniques have moved further along the technology development pipeline.</p> <p>Testing of selected vaccines and diagnostic techniques has taken place.</p> <p>Indian and American scientists have actively collaborated on scientific problems of mutual interest.</p>	<p>The advent of biotechnology has created a potential for vaccine and diagnostic technique development that that didn't exist six years ago.</p> <p>Indian and American scientists are capable of collaborating successfully.</p> <p>AID and the GOI are capable of managing the implementation of the project.</p>
<p><u>Inputs:</u></p> <p>Research support:</p> <p>Technology transfer to Indian scientists and technologists of current techniques in research methodology, disease surveillance, and quality control.</p>	<p>Equipment and supplies have been procured:</p> <p>Indian and U.S. scientists have exchanged visits.</p>	<p>Collaborating U.S. laboratories can procure equipment for Indian counterparts on a timely basis.</p> <p>Indian and U.S. scientists will be able to travel freely and on short notice between the two countries.</p>

ACTION: AID-3 INFO AMB DCM POL ECON-2 USIS PRESS SCI FAS-2 CHRON/14

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LOC: 513 175
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CN: 47876
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Project 386-0503

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PRIORITY

AIDAC

E.O. 12356: N/A
TAGS: N/A
SUBJECT: BIO-IMMUNOLOGY AND DIAGNOSTICS PROJECT
(386-0503)

REF: NEW DELHI 28859

1. AID/W IS DELIGHTED THAT DEVELOPMENT OF SUBJECT PROJECT IS MOVING FORWARD AS WE ALSO SEE THIS AS KEY ELEMENT OF THE VACCINE ACTION PROGRAM (VAP). WE APPRECIATE YOUR EFFORTS TO EXPEDITE DESIGN PROCESS FOR THE SUBJECT PROJECT. BECAUSE OF IMPORTANCE OF THIS ACTIVITY AND SINCE AID/W HAS REVIEWED BASIC SUBSTANCE OF PROJECT IN PREVIOUS PID, WE AGREE WITH MISSION REQUEST TO PROCEED WITH PROJECT DEVELOPMENT WITHOUT ADDITIONAL AID/W REVIEW. HOWEVER, AS YOU ARE AWARE, THERE HAVE BEEN TWO IMPORTANT DEVELOPMENTS SINCE ORIGINAL CONCEPT OF PROJECT WAS DEVELOPED TWO YEARS AGO; THAT IS, THE ESTABLISHMENT OF THE VAP AND NEW AGENCY PRIORITY ON CHILD SURVIVAL. FURTHERMORE, THE MISSION'S OVERALL AND HEALTH PORTFOLIO IN PARTICULAR HAVE BOTH INCREASED IN SIZE AS HAS THE OVERALL MISSION WORKLOAD. BECAUSE OF THESE EVENTS, WE HAVE THREE IMPORTANT CONCERNS, WHICH

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ARE DESCRIBED IN PARAS 2, 3, AND 4 BELOW, AND REQUEST THAT THE MISSION ADDRESS THESE AS THE PROJECT IS DEVELOPED.

2. THE FIRST CONCERN IS WITH MISSION MANAGEMENT CAPABILITIES VS. WORKLOAD AND PROJECT PRIORITIES. MISSION CURRENTLY HAS SOMEWHAT DEMANDING STAFF INTENSIVE PROJECT PORTFOLIO, INCLUDING FOUR HEALTH AND NUTRITION PROJECTS. FURTHERMORE, THE MISSION HAS DEFERRED THE PROPOSED NEW HIGH PRIORITY CHILD SURVIVAL PROJECT UNTIL FY 87. WILL THE PROPOSED PLAN FOR DEVELOPMENT OF THE SUBJECT PROJECT AND THE INCREASED MANAGEMENT BURDEN INTERFERE WITH DEVELOPMENT OF THE CHILD SURVIVAL PROJECT? WHAT ARE MISSION PLANS FOR MANAGEMENT OF SUBJECT PROJECT? WHERE WILL MISSION OBTAIN NECESSARY BIOMEDICAL MEDICAL RESEARCH EXPERTISE? IS MISSION CONSIDERING AN ARRANGEMENT TO CONTRACT FOR THIS LONG TERM EXPERTISE TO HELP MANAGE PROJECT? HOW DOES MISSION PLAN TO MAINTAIN CONTROL OVER PROJECT? WHAT WILL BE ROLE OF EMPASSY SCIENCE ADVISOR AND HHS STAFF IN DESIGN

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AND MANAGEMENT OF SUBJECT PROJECT?

3. WE WOULD LIKE TO BE ASSURED THAT THE RESEARCH FUNDED UNDER THE PROPOSED PROJECT WILL BE SUPPORTIVE OF CHILD SURVIVAL GOALS. WHAT CRITERIA WILL BE ESTABLISHED UNDER THE PROJECT TO ASSURE THAT NEW VACCINES, THERAPEUTICS AND DIAGNOSTICS DEVELOPED UNDER PROJECT ADDRESS THE MAJOR CHILD SURVIVAL DISEASE PROBLEMS?

4. IT IS IMPORTANT THAT PROPOSED PROJECT BE CONSISTENT WITH OTHER AGENCY SUPPORTED BIOMEDICAL RESEARCH EFFORTS AND THAT PROJECT BE DESIGNED IN SOUND SCIENTIFIC BASIS, ESPECIALLY BECAUSE PROJECT IS KEY ELEMENT OF HIGH PROFILE VAP. ST/H AND ANE WILLING TO ASSIST MISSION WITH PROJECT DESIGN OR ANY OTHER PROJECT RELATED NEEDS IF REQUESTED. PLEASE ADVISE.

5. WE REQUEST THAT MISSION ADDRESS ISSUES IN PARA 2, 3 AND 4 IN PP. IN ADDITION, BECAUSE OF HIGH LEVEL INTEREST IN VAP, WE FEEL IT IS IMPORTANT THAT ANE AND ST/H ARE KEPT INFORMED AND AWARE OF PROGRESS AS THE PROPOSED PROJECT IS DEVELOPED AND IMPLEMENTED AND WOULD APPRECIATE MISSION ADVISING AID/W OF PROGRESS. ST/H HAS JUST RECEIVED COPY OF WORKING PAPER ON PROJECT REFERRED TO IN REFTEL AND MAY HAVE ADDITIONAL COMMENTS/REACTIONS WHICH WOULD BE CABLED SEPTEL IN EARLY JANUARY. WHITEHEAD

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ANNEX-III

STANDARD COUNTRY CHECKLIST

COUNTRY CHECKLIST

Listed below are statutory criteria applicable generally to FAA funds, and criteria applicable to individual fund sources: Development Assistance and Economic Support Fund.

A: GENERAL CRITERIA FOR COUNTRY ELIGIBILITY

1. FAA Sec: 481(h) (1); FY 1985 Continuing Resolution Sec. 528. Has it been determined or certified to the Congress by President that the government of the recipient country has failed to take adequate measures or steps to prevent narcotic and psychotropic drugs or other controlled substances (as listed in the schedules in section 202 of the Comprehensive Drug Abuse and Prevention Control Act of 1971) which are cultivated, produced or processed illicitly, in whole or in part, in such country or transported through such country, from being sold illegally within the jurisdiction of such country to United States Government personnel or their dependents or from entering the United States unlawfully? NO.

2. FAA Sec. 481(h) (4). Has the President determined that the recipient country has not taken adequate steps to prevent (a) the processing, in whole or in part, in such country of narcotic and psychotropic drugs or other controlled substances, (b) the transportation through such country of narcotic and psychotropic drugs or other controlled substances, and (c) the use of such country as a refuge for illegal drug traffickers? NO.

3. FAA Sec. 620(c). If assistance is to a government, is the government liable as debtor or unconditional guarantor on any debt to a U.S. citizen for goods or services furnished or ordered where (a) such citizen has exhausted available legal remedies and (b) the debt is not denied or contested by such government? NO.

4. FAA Sec. 620(e)(1). If assistance is to a government, has it (including government agencies or subdivisions) taken any action which has the effect of nationalizing, expropriating, or otherwise seizing ownership or control of property of U.S. citizens or entities beneficially owned by them without taking steps to discharge its obligations toward such citizens or entities? NO.
- 5: FAA Sec: 620(a), 620(f), 620(D); FY 1985 Continuing Resolution Sec 512, and 513.
(a.) Is recipient country a Communist country? (a.) NO.
If so, has the President determined that assistance to the country is important to the national interests of the United States?
(b.) Will assistance be provided to Angola, Cambodia, Cuba, Laos Syria, Vietnam, Libya, or South Yemen? (b.) NO.
(c.) Will assistance be provided to Afghanistan or Mozambique without a waiver? (c.) NO.
- 6: FAA Sec. 620(j). Has the country permitted, or failed to take adequate measures to prevent, the damage or destruction by mob action of U.S. Property? NO.
- 7: FAA Sec. 620(1). Has the country failed to enter into an agreement with OPIC? NO.
8. FAA Sec. 620(o); Fishermen's Protective Act of 1967, as amended, Sec. 5. (a) Has the country seized, or imposed any penalty or sanction against, any U.S. fishing activities in international waters? NO.
- (b) If so, has any deduction required by the Fishermen's Protective Act been made? Not Applicable.

- 9: FAA Sec. 620(g); FY 1985 continuing Resolution Sec. 518. (a.) Has the government of the recipient country been in default for more than six months on interest or principal of any AID loan to the country? (a.) NO.
- (b.) Has the country been in default for more than one year on interest or principal on any U.S. loan under a program for which the appropriation bill (or continuing resolution) appropriates funds? (b.) NO.
10. FAA SEC. 620(s). If contemplated assistance is development loan from Economic Support Fund, has the Administrator taken into account the amount of foreign exchange or other resources which the country has spent on military equipment? (Reference may be made to the annual "Taking Into Consideration" memo: "Yes, taken into account by the Administrator at time of approval of Agency OYB." This approval by the Administrator of the Operational Year Budget can be the basis for an affirmative answer during the fiscal year unless significant changes in circumstances occur.) Not Applicable.
11. FAA Sec. 620(t); Has the country severed diplomatic relation with the United States? If so, have they been resumed and have new bilateral assistance agreements been negotiated and entered into since such resumption? NO.
- 12: FAA Sec. 620(u) What is the payment status of the country's U.N. obligations? If the country is in arrears were such arrearages taken into account by the AID Administrator in determining the current AID Operational Year Budget? (Reference may be made to the Taking into Consideration memo.) India is not in arrears with any U.N. obligations.

FAA Sec. 620A; FY 1985 Continuing Resolution Sec. 521. Has the

President determined that the country (a.) grants sanctuary from prosecution to any individual or group which has committed an act of international terrorism, or (b.) otherwise supports international terrorism? (c.) Has the government of the recipient country aided or abetted by granting sanctuary from prosecution to, any individual or group which has committed or is being sought by any other government for prosecution for any war crime or act of international terrorism?

(a.) NO.

(b.) NO.

(c.) NO.

ISDCA of 1985 Sec. 552(b) Has the Secretary of State determined that the country is a high terrorist threat country after the Secretary of Transportation has determined, pursuant to section 1115(e)(2) of the Federal Aviation Act of 1958, that an airport in the country does not maintain and administer effective security measures?

NO.

FAA Sec. 666. Does the country object, on the basis of race, religion, national origin or sex, to the presence of any officer or employee of the U.S. who is present in such country to carry out economic development programs under the FAA?

NO.

FAA Sec. 669, 670 Has the country, after August 3, 1977, delivered or received nuclear enrichment or re-processing equipment, materials, or technology, without specified arrangements or safeguards? Has it transferred a nuclear explosive device to a non-nuclear weapon state, or if such a state, either received or detonated a nuclear explosive device? (FAA Sec 620E permits a special waiver of Sec. 669 for Pakistan.)

India has received no such equipment, materials, or technology without specified safeguards. Based on information from the State Department, the answer to the second question is also no.

14. FAA Sec. 620A; FY 1985 Continuing Resolution Sec. 521. Has the President determined that the country (a.) grants sanctuary from prosecution to any individual or group which has committed an act of international terrorism, or (b.) otherwise supports international terrorism? (c.) Has the government of the recipient country aided or abetted by granting sanctuary from prosecution to, any individual or group which has committed or is being sought by any other government for prosecution for any war crime or act of international terrorism?
- (a.) NO.
(b.) NO.
(c.) NO.
15. ISDCA of 1985 Sec. 552(b) Has the Secretary of State determined that the country is a high terrorist threat country after the Secretary of Transportation has determined, pursuant to section 1115(e)(2) of the Federal Aviation Act of 1958, that an airport in the country does not maintain and administer effective security measures?
- NO.
- 16: FAA Sec. 666. Does the country object, on the basis of race, religion, national origin or sex, to the presence of any officer or employee of the U.S. who is present in such country to carry out economic development programs under the FAA?
- NO.
17. FAA Sec. 669, 670 Has the country, after August 3, 1977, delivered or received nuclear enrichment or re-processing equipment, materials, or technology, without specified arrangements or safeguards? Has it transferred a nuclear explosive device to a non-nuclear weapon state, or if such a state, either received or detonated a nuclear explosive device? (FAA Sec 620E permits a special waiver of Sec. 669 for Pakistan.)
- India has received no such equipment, materials, or technology without specified safeguards. Based on information from the State Department, the answer to the second question is also no.

18. FAA Sec. 670. If the country is a non-nuclear weapon state, has it, on or after August 8, 1985, exported illegally (or attempted to export illegally) from the United States any material, equipment, or technology which would contribute significantly to the ability of such country to manufacture a nuclear explosive device?

Not Applicable.

19. ISDCA of 1981 Sec. 720. Was the country represented at the Meeting of Ministers of Foreign Affairs and Heads of Delegations of the Non-Aligned Countries to the 36th General Assembly of the U.N. of Sept. 25 and 28, 1981, and failed to disassociate itself from the communique issues? If so, has the President taken it into account? (Reference may be made to the Taking into Consideration memo.)

Although the GOI has failed to disassociate itself from the communique, the Administrator has taken this into account in the OYB allocation process.

20. FY 1985 Continuing Resolution. If assistance is from the population functional account, does the country (or organization) include as part of its population planning programs involuntary abortion?

NO.

21. FY 1985 Continuing Resolution Sec. 530. Has the recipient country been determined by the President to have engaged in a consistent pattern of opposition to the foreign policy of the United States?

NO.

B. FUNDING SOURCE CRITERIA FOR COUNTRY ELIGIBILITY

1. Development Assistance Country Criteria

FAA Sec. 116 Has the Department of State determined that this government has engaged in a consistent pattern of gross violations of internationally recognized human rights? If so, can it be demonstrated that contemplated assistance will directly benefit the needy? NO.

ANNEX-IV

STANDARD PROJECT CHECKLIST

PROJECT CHECKLIST

Listed below are statutory criteria applicable to projects. This section is divided into two parts. Part A includes criteria applicable to all projects. Part B applies to projects funded from specific sources only: B.1. applies to all projects funded with Development Assistance loans, and B.3. applies to projects funded from ESP.

CROSS REFERENCES: IS COUNTRY CHECKLIST UP-TO-DATE? YES.

HAS STANDARD ITEM CHECKLIST
BEEN REVIEWED FOR THIS PROJECT?

A. GENERAL CRITERIA FOR PROJECT

1. FY 1985 Continuing Resolution
Sec 525; FAA Sec. 634A.

Describe how authorizing and appropriations committees of Senate and House have been or will be notified concerning the project.

A Congressional Notification will be forwarded prior to the initial obligation of funds.

2. FAA Sec. 611(a)(1): Prior to obligation in excess of \$500,000 will there be (a.) engineering, financial and other plans necessary to carry out the assistance and (b.) a reasonably firm estimate of the cost to the U.S: of the assistance?
- (a.) YES:
(b.) YES.

3. FAA Sec. 611(a)(2). If further legislative action is required within recipient country, what is basis for reasonable expectation that such action will be completed in time to permit orderly accomplishment of purpose of the assistance?
- Not Applicable.

4. FAA Sec. 611(b); FY 1985 Continuing Resolution Sec. 501. If for water or water-related land resource construction, has project met the principles, standards and procedures established pursuant to the Water Resources Planning Act (42 U.S.C. 1962, et seq.)? (See AID Handbook 3 for new guidelines)
- Not Applicable.

5. FAA Sec: 611(e). If project is capital assistance (e.g., construction), and all U.S. assistance for it will exceed \$1 million, has Mission Director certified and Regional Assistant Administrator taken into consideration the country's capability to effectively maintain and utilize the project? Not Applicable.
6. FAA Sec. 209. Is project susceptible to execution as part of regional or multilateral project? If so, why is project not so executed? Information and conclusion whether assistance will encourage regional development programs. This project is not susceptible to execution as part of a regional or multilateral program.
- 7: FAA Sec: 601(a). Information and conclusions whether project will encourage efforts of the country to: (a) increase the flow of international trade; (b) foster private initiative and competition; (c) encourage development and use of cooperatives, credit unions, and savings and loan associations; (d) discourage monopolistic practices; (e) improve technical efficiency of industry, agriculture and commerce and (f) strengthen free labor unions: (a) Not Applicable.
(b) Not Applicable.
(c) Not Applicable.
(d) Not Applicable.
(e) Not Applicable.
(f) Not Applicable.
8. FAA Sec. 601(b). Information and conclusion on how project will encourage U.S. private trade and investment abroad and encourage private U.S. participation in foreign assistance programs (including use of private trade channels and the services of U.S. private enterprise). U.S. private sector biotechnology firms are eligible to participate in the project if they identify an Indian collaborator.
- 9: FAA Sec: 612(b); Sec: 636(h); FY 1985 Continuing Resolution Sec. 507 Describe steps taken to assure that, to the maximum extent possible, the country is contributing local currencies to meet the cost of contractual and other services, and foreign currencies owned by the U.S. are utilized in lieu of dollars The Government of India will contribute more than 25 percent of local costs.

10. FAA Sec. 612(d): Does the U.S. own excess foreign currency of the country and if so, what arrangements have been made for its release?
- U.S. owned rupees are being used for various U.S. Government agencies' programs and for administrative support. India will shortly be declared a "near excess" contry.
11. FAA Sec. 601(e). Will the project utilize competitive selection procedures for the awarding of contracts, except where applicable procurement rules allow otherwise?
- YES.
12. FY 1985 Continuing Resolution Sec. 522.
If assistance is for the production of any commodity for export, is the commodity likely to be in surplus on world markets at the time the resulting productive capacity becomes operative, and is such assistance likely to cause substantial injury to U.S. producers of the same, similar or competing commodity.
- Not Applicable.
13. FAA 118(c) and (d). (a.) Does the project comply with the environmental procedures set forth in AID Regulation 16. (b.) Does the project or program take into consideration the problem of the destruction of tropical forests?
- (a.) YES.
(b.) Not Applicable.
14. FAA 121(d). If a Sahel project, has a determination been made that the host government has an adequate system for accounting for and controlling receipt and expenditure of project funds (dollars or local currency generated therefrom)?
- Not Applicable.
15. FY 1985 Continuing Resolution Sec. 536. Is disbursement of the assistance conditioned solely on the basis of the policies of any multilateral institution?
- NO.

16: ISDCA of 1985 Sec. 310. For development assistance projects, how much of the funds will be available only for activities of economically and socially disadvantaged enterprises, historically black colleges and universities, and private and voluntary organizations which are controlled by individuals who are black Americans, Hispanic Americans, or Native Americans, or who are economically or socially disadvantaged (including women)?

Given the nature of the project, this information will not be available until project proposals are generated.

I. FUNDING CRITERIA FOR PROJECT

1. Development Assistance Project Criteria

a : FAA Sec. 102(a); 111, 113, 281(a) Extent to which activity will (a.) effectively involve the poor in development, by extending access to economy at local level, increasing labor-intensive production and the use of appropriate technology, spreading investment out from cities to small towns and rural areas, and insuring wide participation of the poor in the benefits of development on a sustained basis, using the appropriate U.S. institutions; (b.) help develop co-operatives, especially by technical assistance, to assist rural and urban poor to help themselves toward better life, and otherwise encourage democratic private and local governmental institutions; (c.) support the self-help efforts of developing countries; (d.) promote the participation of women in the national economies of developing countries and the improvement of women's status; and (e.) utilize and encourage regional cooperation by developing countries?

(a.) This project will support the development of vaccine and diagnostic techniques that will improve the health and well being of the poor.

(b.) Not Applicable.

(c.) This project entirely supports Indian self help by building up research capabilities:

(d.) Women scientists will actively participate in the project.

(e.) Not Applicable.

- b: FAA Sec. 103, 103A, 104, 105, 106: Does the project fit the criteria for the type of funds (functional account) being used? This project fits the criteria for section 104 funds.
- c: FAA Sec. 107: Is emphasis on use of appropriate technology (relatively smaller, cost-saving, labor-using technologies that are generally most appropriate for the small farms, small businesses, and small incomes of the poor)? Yes, particularly for rapid diagnostic techniques.
- d. FAA Sec. 110(a). Will the recipient country provide at least 25% of the costs of the program, project, or activity with respect to which the assistance is to be furnished (or is the latter cost-sharing requirement been waived for a "relatively least-developed country)? YES.
- e. FAA Sec. 122(b). Does the activity give reasonable promise of contributing to the development of economic resources, or to the increase or productive capacities and self-sustaining economic growth? YES.
- f. FAA Sec. 128(b) If the activity attempts to increase the institutional capabilities of private organizations or the government of the country, or if it attempts to stimulate scientific and technological research, has it been designed and will it be monitored to ensure that the ultimate beneficiaries are the poor majority? YES.
- g. FAA Sec. 281(b): Describe extent to which program recognizes the particular needs, desires and capacities of the people of the country; utilizes the country's intellectual resources to encourage institutional development; and supports civil education and training in skills required for effective participation in governmental and political processes essential to self-government. The health status of the Indian people is cause for serious concern. An effective way of improving the health status is to develop new and improved vaccines and immunodiagnostic techniques. This project will take advantage of the country's intellectual resources to conduct research in the fields of vaccines and diagnostics.

STANDARD ITEM CHECKLIST

Listed below are the statutory items which normally will be covered routinely in those provisions of an assistance agreement dealing with its implementation, or covered in the agreement by imposing limits on certain uses of funds.

These items are arranged under the general headings of (A) Procurement, (B) Construction, and (C) Other Restrictions.

A. Procurement

1. FAA Sec. 602. Are there arrangements to permit U.S. small business to participate equitably in the furnishing of commodities and services financed? YES.

- 2: FAA Sec. 604(a) Will all procurement be from the U.S. except as otherwise determined by the President or under delegation from him? All procurement will be from the U.S. or India unless otherwise agreed.

3. FAA Sec. 604 (d): If the cooperating country discriminates against marine insurance companies authorized to do business in the U.S., will commodities be insured in the United States against marine risk with such a company? The country does not so discriminate.

- 4: FAA Sec. 604(e); ISDCA of 1980 Sec. 705(a). If offshore procurement of agricultural commodity or product is to be financed, is there provision against such procurement when the domestic price of such commodity is less than parity? (Exception where commodity financed could not reasonably be procured in U.S.?) Not Applicable.

- 5: FAA Sec. 604(g). Will construction or engineering services be procured from firms of countries which receive direct economic assistance under the FAA and which are otherwise eligible under Code 941, but which have attained a competitive capability in international markets in one of these areas? Do these countries permit United States firms to compete for for construction or engineering services financed from assistance programs of these countries?
- Not Applicable.
6. FAA Sec. 603. Is the shipping excluded from compliance with requirement in Section 901(b) of the Merchant Marine Act of 1936, as amended, that at least 50 per centum of the gross tonnage of commodities (computed separately for dry bulk carriers, dray cargo liners, and tankers) financed shall be transported on privately owned U.S. flag commercial vessels to the extent such vessels are available at fair and reasonable rates?
- Shipping is not excluded from compliance with Section 901(b).
7. FAA Sec. 621 If technical assistance is financed, will such assistance be furnished by private enterprise on a contract basis to the fullest extent practicable? If the facilities of other Federal agencies will be utilized, are they particularly suitable, not competitive with private enterprise, and made available without undue interference with domestic programs?
- Technical assistance will be provided by the U.S. Public Health Service and meets the criteria outlined in sentence two.

8: International Air Transportation Fair Competitive Practices Act, 1974. If air transportation of persons or property is financed on grant basis, will U.S. carriers be used to the extent such service is available? YES:

9: FY 1985 Continuing Resolution Sec. 504. If the U.S. Government is a party to a contract for procurement, does the contract contain a provision authorizing termination of such contract for the convenience of the United States? YES.

B: Construction

1. FAA Sec. 601(d). If capital (e.g. construction) project, will U.S. engineering and professional services be used? Not Applicable.

2. FAA Sec. 611(c) If contracts for construction are to be financed, will they be let on a competitive basis to maximum extent practicable? Not Applicable.

3: FAA Sec. 620(k) If for construction of productive enterprise, will aggregate value of assistance to be furnished by the U.S. not exceed \$100 million (except for productive enterprises in Egypt that were described in the CP)? Not Applicable.

C. Other Restrictions

1. FAA Sec. 122(b) If development loan, is interest rate at least 2% per annum during grace period and at least 3% per annum thereafter? Not Applicable:

SB

2. FAA Sec. 301(d) If fund is established solely by U.S. contributions and administered by an international organization, does Comptroller General have audit rights? Not Applicable.
3. FAA Sec. 620(h) Do arrangements exist to insure that United States foreign aid is not used in a manner which, contrary to the best interests of the United States, promotes or assists the foreign aid projects or activities of the Communist-bloc countries? YES.
4. Will arrangements preclude use of financing:
- a. FAA Sec. 104(f); FY 1985
Continuing Resolution Sec. 527
- (1) To pay for performance of abortions as a method of family planning or to motivate or coerce persons to practice abortions; (1) YES.
- (2) to pay for performance of involuntary sterilization as method of family planning, or to coerce or provide financial incentive to any person to undergo sterilization; (2) YES.
- (3) to pay for any biomedical research which relates, in whole or part, to methods or the performance of abortions or involuntary sterilizations as a means of family planning; (3) YES.
- (4) to lobby for abortion? (4) YES.
- b. FAA Sec. 483: To reimburse persons, in the form of cash payments, whose illicit drug crops are eradicated? YES.
- c. FAA Sec. 620(g). To compensate owners for expropriated nationalized property? YES.

- d. FAA Sec. 660. To provide training or advice or provide any financial support for police, prisons, or other law enforcement forces, except for narcotics programs? YES.
- e. FAA Sec. 662. For CIA activities? YES.
- f. FAA Sec. 636(1): For purchase, sale, long-term lease, exchange or guaranty of the sale of motor vehicles manufactured outside U.S., unless a waiver is obtained? YES.
- g. FY 1985 Continuing Resolution, Sec. 503. To pay pensions, annuities, retirement pay, or adjusted service compensation for military personnel? YES.
- h. FY 1985 Continuing Resolution, Sec. 506: To carry out provisions of FAA Section 209(d) (Transfer of FAA funds to multilateral organizations for lending)? YES.
- j. FY 1985 Continuing Resolution, Sec. 510: To finance the export of nuclear equipment, fuel, or technology or to train foreign nationals in nuclear fields? YES.
- k. FY 1985 Continuing Resolution, Sec. 511. Will assistance be provided for the purpose of aiding the efforts of the government of such country to repress the legitimate rights of the population of such country contrary to the Universal Declaration of Human Rights? Such assistance will not be provided.
- l. FY 1985 Continuing Resolution, Sec. 516: To be used for publicity or propaganda purposes within U.S. not authorized by Congress? Such purposes will not be financed.

ANNEX-V

DESCRIPTION OF CENTERS FOR DISEASE CONTROL PARTICIPATION
IN THE CREATION OF THE CENTRE FOR EPIDEMIOLOGIC
RESEARCH AND TRAINING

AIRGRAM

PO50158-1482

DEPT. DISTRIBUTION ORIGIN/ACTION				HANDLING <i>(24)</i>	CLASSIFICATION UNCLASSIFIED	MESSAGE REFERENCE NO A-686
<i>HHS</i>				<p>TO: AMEMBASSY NEW DELHI</p> <p>FROM: DEPARTMENT OF STATE</p> <p>E.O. 11652: N/A</p> <p>TAGS: TBIO, TPHY, OSCI, IN</p> <p>SUBJECT: U.S.-INDO VACCINE ACTION PROGRAM - PROJECT 01-344-C DEVELOPMENT OF VACCINE-PREVENTABLE DISEASE STUDY CENT</p> <p>REF:</p> <p>Enclosed are two copies of the project description and the obligating document for SFCP supported project number 01-344-C, "Development of Vaccine Preventable Disease Study Center." This Project is a collaboration between the DHHS/PHS Centers for Disease Control and the Tuberculosis Research Center of the Indian Council for Medical Research.</p> <p>This project was recommended by the U.S.-Indo S & T Subcommittee at its April 1985 meeting. It was subsequently incorporated in to plan for the Vaccine Action Program, which was announced by President Reagan and Prime Minister Gandhi in July.</p> <p>Embassy is requested to pass the technical portion of the document to the ICMR with the request that they comment and advise when it will be convenient for the U.S. Collaborator to meet with counterparts in India. No signatures are required on this document.</p> <p>All expenditures for the first year will be for U.S. uses - principally to support transportation and related expenses of U.S. experts.</p> <p style="text-align:right;"><i>-attached</i> SHULTZ</p> <p>Enclosures: 01-344-C (2)</p> <p style="text-align:right;">UNCLASSIFIED CLASSIFICATION</p>		
AF	ARA	BF/OB	CU			
D/HA	D/LOS	EA	EB			
EUR	FADRC/OR	FADRC/LR	FBO			
IGA	INR	IO	L			
M/MO	MC	NEA	OES			
PER	PM	PPT	S/IL			
S/NM	S/P	S/PRS	S/S			
SCA	SCS	SY	VO			
Suggested Distribution						
POST ROUTING						
TO:	ACTION	INFO				
AMB						
DCM						
POL						
ECON						
COMM'L						
USIS						
AGR						
AID						
DAO						
CONS						
ADM						
B&F						
GSO						
PER						
SY						
C&R						
DRAFTED BY: DHHS/PHS/OIH:LVOGEL <i>LV</i>				DRAFTING DATE: 9/30/85	PHONE NO.: 443-1774	CONTENTS AND CLASSIFICATION APPROVED BY: OES/SCT:DJAMESON

CLEARANCES:

OES/SCT:RFPost : OES/ENH:Wwalsh(Info) NEA/INS: DCamp (INFO)
AID/BST/H:KBart(Info) Wh OSTP:Wince(Info)

OPTIONAL FORM 247 (Rev. 5-82)
DEPARTMENT OF STATE
50247-102

57

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE**

SCIENTIFIC ACTIVITIES OVERSEAS (Special Foreign Currency Program)

0 1 - 3 4 4 - C
PROJECT NUMBER

An Agreement Providing for the conduct of a Project described herein under Section 104(b)(3) of Public Law 83-480, as amended, and Section 307 of the Public Service Act, between the United States of America as represented by the Centers for Disease Control, DHHS, DMHS, authorized by the signature below, and TRC Field Study, Trivullore, authorized by the signatures below.

SHORT DESCRIPTIVE TITLE: DEVELOPMENT OF VACCINE-PREVENTABLE DISEASE STUDY CENTER

PERIOD OF AGREEMENT 5 years YEARS

PROPOSED PROJECT PERIOD 3/1/86 TO 3/1/91

TYPE OF AGREEMENT

- NEW
 AMENDMENT (NO.)
 SUPPLEMENT
 CONTINUATION

PUBLIC HEALTH SERVICE
AGENCY: Centers for Disease Control
PROGRAM: Center for Prevention Services

PROJECT OFFICER & TITLE

Steven Wassilak, M.D.
 Division of Immunization
 Center for Prevention Services
 Centers for Disease Control

AUTHORIZING SIGNATURES:

Billy L. Hays
 Acting Assistant Director for
 International Health, CDC

TITLE _____ DATE Sept. 27, 1985

C. Everett Koop, M.D.
 Surgeon General and
 Director, Office of International Health

TITLE _____ DATE Sept. 30, 1985

AGREEMENT AMOUNT (In local currency)

PROJECT Rs. 10,000,000

INT'L TRAVEL 1,400,000

AUDIT _____

TOTAL Rs. 11,400,000

AMOUNT OF INCREASE OR DECREASE

PROJECT _____

INT'L TRAVEL _____

SUB-TOTAL _____

Revised TOTAL _____

COLLABORATING INSTITUTION:

Tuberculosis Research Center
 Indian Council for Medical Research
 Trivullore
PRINCIPAL INVESTIGATOR (NAME AND TITLE):
 Dr. V. Ramalingaswami
 Director General
 Indian Council for Medical Research

AUTHORIZING SIGNATURES:

N/A This document is for U.S.
accounting purposes only

TITLE _____ DATE _____

TITLE _____ DATE _____

FOR ADMINISTRATIVE USE ONLY
 \$ 914,194 (DOLLAR EQUIVALENT)

ORIGINAL _____
 INC. OR DECR. _____
 TOTAL _____

75X1102
 APPROPRIATION

0 1 344 85 A731901 --- 25 31
 COUNTRY PROJ. FY CAN O.C.

Effective month of obligation _____

PAYEE OR FINANCIAL OFFICER

NAME _____

TITLE Indian Council for Medical Research

ADDRESS _____

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL

An Agreement Providing for the Conduct of Research Under
Section 104(b)(3) of Public Law 83-480, as Amended and
Section 308 of the Public Health Service Act

Agreement 01-344-C

Parties to the Agreement:

1. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Atlanta, Georgia
2. Tuberculosis Research Center, Indian Council for Medical Research, Trivullore, India.

Purpose of Work to be Carried Out:

Development of Vaccine-Preventable Disease Study Center as a Component of the U.S.-Indo Vaccine Action Program

Effective Period of Project:

Five years March 1, 1986 - March 1, 1991

Total Funds to be Provided During Project Period:

11,400,000 Rupees

U.S. Collaborating Institute:

Project Collaborators:

Steven Wassilak, M.D.
Division of Immunization
Center for Prevention Services
Centers for Disease Control

Indian Collaborating Institute:

Project Officer:

V. Ramalingaswami, M.D.
Director General
Indian Council for Medical
Research

United States Government
Department of Health and Human Services
Public Health Service

Agreement No. 01-344-C

Centers for Disease Control

This document provides for a project to be carried out under the authorities provided by Section 104(b) (3) of Public Law 83-480, as amended; and Section 308 of the Public Health Service Act

This Project is to be carried out jointly between the Centers for Disease Control, Public Health Service, Department of Health and Human Services, United States of America, and the Tuberculosis Research Center, Indian Council for Medical Research, Trivullore, India.

This document consists of three Parts: (1) Project Description, (2) Budget, (3) General Provisions.

PART I

Proposal for the Development of a Vaccine-Preventable Disease Study Center at Trivullore

This is a proposal to undertake the development of a Vaccine-Preventable Disease Study Center (VPDSC) in India, which would help implement various components of the Vaccine Action Program (VAP). Funds for travel and data collection are being sought for this development project to ensure that several elements of the Vaccine Action Program can be applied to populations broader than currently addressed by Agency for International Development activities. Specifically, adults and children over the age of four are potential recipients of the new vaccines which would be evaluated by the program.

BACKGROUND

As a continuation of the advances made under the Indo-US Science and Technology Initiative, a proposal has been put forth to establish an Indo-US Cooperative Vaccine Development Action Program, identified as the VAP. The elements of this proposed program have been endorsed by the Seventh Session of the Indo-US Science and Technology Subcommission. Preliminary planning of the program's implementation was undertaken through a meeting of representatives of both governments in Bethesda, Maryland on May 7, 1985.

VAP is a collection of initiatives designed to substantially reduce the burden of diseases in India by the application and development of biotechnology in vaccine research. The elements of the VAP proposal are:

1. Vaccine Research and Development
 - a. Increasing and targeting basic research in biotechnology with the goal of obtaining vaccines that could be applied for wide use.
 - b. Undertaking field studies for safety, immunogenicity, and efficacy of newly developed vaccines that are currently ready for such study or that, as a result of continuing basic research, are developed and become feasible for use.
 - c. Reinforcing current activities in quality control of vaccine production so that large-scale production of safe and effective products can be fully realized.

2. Diagnostic technology development

Develop immunodiagnostic and other laboratory diagnostic technologies to support the epidemiologic research necessary for the establishment of development priorities and to support the field studies resulting from VAP technological advances.

3. Epidemiology and vaccine delivery

- a. Through careful studies, assess the burden of diseases which could be vaccine-preventable with further biotechnical advances so that priorities can be clearly reached in vaccine development research.
- b. Establish a population laboratory for the continual assessment of the epidemiology of vaccine-preventable diseases when vaccination is in place and to assess the programmatic aspects of vaccine delivery.
- c. Study various technical issues which affect the use of vaccines, such as stability, alternate routes of administration, mixing of vaccines, etc.

4. Training

In all components, an exchange of information with on site personnel will be fully pursued.

Through all components of VAP, a comprehensive approach to vaccine research will be realized that will benefit India and all other areas of the world where VAP successes can be applied. This current proposal is being made to develop a Vaccine-Preventable Disease Study Center (VPDSC) that will help implement several elements of VAP.

OBJECTIVES

The goal of VPDSC would be to provide needed information about vaccine preventable diseases and vaccines which may be used to improve disease control or prevention. A single study center for the study of several diseases and vaccines would provide an avenue for a cohesive approach to several elements of VAP. Over the initial two years, this project seeks specifically to:

1. Identify the elements necessary to establish a VPDSC in concert with Indian Health Authorities.
2. Identify a stable, well-defined population or populations in which epidemiologic studies can be carried out.
3. Examine the available baseline demographic data and assess the currently available epidemiologic information on diseases currently preventable by vaccination or potentially preventable by new vaccines.
4. Identify and/or train the personnel necessary for more detailed collection of epidemiologic data on diseases currently preventable by vaccination or subject to being preventable with technologic advances.

5. Carry out selected studies needed to accurately delineate the characteristics of polio, measles, tetanus, diphtheria, and pertusis in the defined population.
6. Evaluate the effectiveness of vaccines and vaccination programs in current use in the defined population.
7. Assist in the necessary studies, including the evaluation of new diagnostic tests, to accurately delineate the epidemiology of other diseases against which newly developed vaccines could be used.

When the VPDSC is established, further objectives of VPDSC would be to:

1. Assess the safety and efficacy of any newly developed vaccines which may be adopted for future use. Likely candidates include vaccines against invasive Haemophilus influenzae disease, hepatitis A and B, influenza, malaria, meningococcal disease, pertussis, respiratory syncytial virus, rotavirus, and bacterial enteric pathogens.
2. Make available any information collected for possible use in developing or modifying vaccination policies or in vaccine delivery.

Ongoing travel and examination of data would be necessary over a five year period for the establishment and maintenance of a fully active VPDSC.

The Tuberculosis Study Center (TRC) at Madras has been suggested as a potential collaborator in VPDSC; the TRC Trivullore study area has a large rural population about which an extensive collection of demographic information exist, and TRC possesses technical and scientific personnel fully capable of expeditiously establishing a comprehensive study center as an extension of current activities.

The VPDSC would implement fully or partially the elements of VAP identified above as 1b, 3a, 3b, 3c, and 4.

METHODS

Meetings will be set up with members of the Indian Ministry of Health, the Indian Council for Medical Research, and the Tuberculosis Study Center for an initial exploratory visit and thorough examination of the resources and data available. This will be accomplished by a team of two medical epidemiologists and a program manager. A specific protocol and timetable will be derived as a result of this meeting. Subsequently, three trips per year will be necessary to fulfill each of the specific objectives above in sequence. Planning for the initiation of further epidemiologic studies and clinical field testing of new vaccines would proceed during the implementation of the initial objectives. At the end of two years, the initial 6 objectives above should be reached, and implementation of subsequent objectives could be initiated. A representative of the Indian collaborating institution will need to visit with collaborators in the US yearly for visits with other key personnel involved

with VAP as well as to pursue the possibilities of testing vaccines developed outside of India which would be candidates for use in India.

PART II

BUDGET

Proposed Travel:

<u>Project Year</u>	<u>No. of Persons</u>	<u>Origin</u>	<u>Destination</u>	<u>No. of Weeks</u>
1	3	U.S.	Dehli/Madras	3
1	1	U.S.	VPDSC	2
1	1	U.S.	VPDSC	2
1	1	U.S.	VPDSC	2
2	1	U.S.	VPDSC	2
2	1	U.S.	VPDSC	2
2	1	U.S.	VPDSC	2
2	1	India	U.S.	2
3	1	U.S.	VPDSC	2
3	1	U.S.	VPDSC	2
3	1	U.S.	VPDSC	2
3	1	India	U.S.	2
4	1	U.S.	VPDSC	2
4	1	U.S.	VPDSC	2
4	1	U.S.	VPDSC	2
4	1	India	U.S.	2
5	1	U.S.	VPDSC	2
5	1	U.S.	VPDSC	2
5	1	U.S.	VPDSC	2
5	1	India	U.S.	2

In addition, \$500,000 would be necessary in the first two years of the project for the collection of baseline epidemiologic information on diseases currently preventable by vaccination or potentially preventable by new vaccines, to identify and/or train the personnel necessary for more detailed collection of epidemiologic data of diseases currently preventable by vaccination or subject to being preventable with technologic advances and to evaluate the effectiveness of vaccines and vaccination programs in current use in the defined population. Subsequent maintenance of core VPDSC activities will require \$100,000 per year for the remaining three years proposed for VPDSC development, as clinical trials and further epidemiologic data collection are initiated.

SFCP Budget:

Project: Rps. 10,000,000

Int'l Travel: 1,400,000

GRAND TOTAL: Rps. 11,400,000

**PART III
GENERAL PROVISIONS**

A. GENERAL UNDERSTANDING

1. It is the intent of the parties to this Agreement to provide for the conduct of the research and related activities as set forth in Part I as being of mutual interest to both countries in the advancement of their respective scientific and health objectives.
2. The U.S. Collaborating Institution agrees to make payment in local currencies in an amount not to exceed Rs. 10,000,000 for the performance of the research by the Indian Collaborating Institution, to be paid as specified in subagreements which will become annexes to this agreement.
3. The Indian Collaborating Institution agrees to utilize such funds solely for the purpose of carrying out the research activities set forth in Part I in accordance with the terms and conditions hereinafter specified, and to accept payment in local currencies in the amount specified.
4. Funds paid to the Indian Collaborating Institution under this Agreement will, in accordance with U.S. Government regulations, be placed in a non-interest-bearing account.

B. RESPONSIBILITIES OF THE INDIAN COLLABORATING INSTITUTION

1. Organization and performance of the research plan provided in Part I, in collaboration with the Centers for Disease Control, U.S. Department of Health and Human Services.
2. Appointment of qualified personnel to work on the research project as detailed in Part I.
3. Provision of facilities and working space for staff.
4. Preparation and submission of the project reports as specified in this Agreement.
5. Such commitments as are defined in this Agreement.

C. RESPONSIBILITIES OF THE U.S. COLLABORATING INSTITUTION

1. Periodic review of the performance and results of the research plan.
2. Notification through proper channels to the U.S. Embassy for periodic payments within the terms of this Agreement.
3. Participation with the Indian Collaborating Institution in the dissemination of research results.
4. Any other commitments as are defined in this Agreement.

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D. CHANGES IN RESPECTIVE RESPONSIBILITIES OF RESEARCH PLANS

Since the course of any scientific investigation is not entirely predictable, on the basis of findings or other considerations, a change in approach or techniques used may be made after appropriate consultation between the Indian Project Officer and the U.S. Collaborating Institution.

E. COMPENSATION

1. Budget Plan

Funds will be advanced to the Indian Collaborating Institution for expenditures necessary for research activities set forth in the Budget Plan (PART II). Expenditures shall be made in accordance with the budget plan.

2. Changes in Budget Plan

Any circumstances which in the opinion of the Indian Project Officer will require a modification of more than ten percent from each of the approved estimated items of expenditure will require prior approval of the U.S. Collaborating Institution.

F. METHOD OF PAYMENT

1. Advance Payment

Upon signing of this Agreement by both parties, the U.S. Collaborating Institution will make an advance payment to the Indian Collaborating Institution to begin this program.

2. Succeeding Payment

Three months prior to the completion of the first year/subsequent year of the project scheme, the Indian Collaborating Institutions will send the estimate of expenditure for the second year/subsequent year together with a summary of the research work done and the expenditure incurred/likely to be incurred in the first year/subsequent year to the U.S. Embassy with the request for release of funds for the second/subsequent year to keep the project scheme going. The Indian Collaborating Institution will supply to the U.S. Collaborating Institution such further information regarding the research scheme as the U.S. Collaborating Institution may reasonably request for releasing subsequent installments of the award funds.

3. Project-Related Income

Any income derived from the work carried out under this Agreement shall be reported by the Indian Collaborating Institution on its annual

General Provisions - Continued - Page 3

financial report. It is mutually agreed that such income will be used to further the purposes of this project.

4. Unexpended Balance

The Indian Collaborating Institution agrees to return without delay any unexpended balance in the project in its possession at the end of the Agreement period or the termination of the project, whichever comes first, to the U.S. Embassy without demand. The amount to be returned, if any, will be determined by the U.S. Collaborating Institution after review of the final financial report and consultation with the Indian Collaborating Institution.

G. RECORDS

1. The Indian Collaborating Institution agrees to keep adequate records for documentation of progress made and status of this project as well as for preparation of reports on the scientific aspects of this program; and further agrees to keep records of obligations and expenditures, together with receipts, vouchers, correspondence and memoranda associated with funds received and expended in carrying out the research provided for in this Agreement.

2. Such records shall be retained by the Indian Collaborating Institution until the final audit report is accepted and any audit questions are resolved to the satisfaction of the U.S. Collaborating Institution.

3. Accounts of expenditures incurred on the research scheme will be audited annually by a Chartered Accountant and an audited statement of accounts will be submitted by the Indian Project Officer. A copy thereof will be supplied to the U.S. Collaborating Institution through the American Embassy.

H. REPORTS

1. Financial Reports

Financial reports covering expenditures actually incurred on the research scheme during a one-year period will be submitted annually.

On completion or termination of the project, whichever comes first, a final report of expenditures for the entire research scheme will be submitted.

2. Technical Reports

As specified in Part F, Item 2 above, a summary of the research work done will be submitted three months prior to the completion of each project year. Interim reports or information on the progress of the

work will be submitted as necessary in connection with special events or problems during the course of the work.

At the conclusion of the Agreement, a final report will be submitted in a form suitable for publication, including all pertinent technical data and summarizing the work done, the results accomplished and the conclusions drawn therefrom.

All reports and other communications will be transmitted in the English language.

I. ACCESS TO FACILITIES, RECORDS AND ACCOUNTS

The accredited representatives of the U.S. Collaborating Institution will, on reasonable advance notice to the Indian Collaborating Institution, be allowed access to that part of the research facilities or offices utilized in connection with the research project described in this Agreement for the purpose of observing the status and progress of this project.

J. EQUIPMENT, SUPPLIES AND MATERIALS

Equipment and unconsumed supplies and materials remaining at the completion of or termination of the project will be disposed of at the direction of the U.S. Collaborating Institution after appropriate negotiation with the Indian Collaborating Institution. An inventory of remaining supplies and equipment must be submitted with the financial report.

K. PUBLICATIONS AND PATENTS

1. Publications

Publications and copyrighting of findings shall be at the discretion of the Indian Collaborating Institution and shall be in accordance with the policy of the Government of India. The U.S. Collaborating Institution reserves a royalty-free, non-exclusive, irrevocable license to reproduce, translate, publish, use, and to authorize others to do so, all copyrightable or copyrighted material generated by the investigation. At least one copy of any publication resulting from work supported under this Agreement will be provided to the U.S. Collaborating Institution. Acknowledgement of the U.S. collaboration should be made by the following or a comparable footnote: "This investigation was conducted in collaboration with the Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services, under Agreement No. 01-344-C, as an activity of the Indo-U.S. Vaccine Action Program."

2. Patents

All inventions conceived or first actually reduced to practice in performance of the investigation shall be reported to the Government of India/DAE and the U.S. Collaborating Institution for disposition in accordance with the policies of both countries as specified below. The ownership and manner of disposition of all rights in such inventions in India and all other countries except the United States shall be for determination by the Government of India, subject to a non-exclusive, non-transferable, paid-up license to make, use and sell such inventions throughout the world by or on behalf of the Government of the United States. The ownership and manner of disposition of all rights in such inventions in the United States shall be determined by the U.S. Collaborating Institution.

With respect to patentable results and in accordance with the foregoing paragraph, the Indian Collaborating Institution agrees to cooperate in the preparation and prosecution of any United States patent application, to execute all papers requisite to such prosecution, and to secure the cooperation of any of its employees in the preparation and prosecution of such papers.

L. RESEARCH ASSISTANCE

Contracts or other agreements will not be made by the Indian Collaborating Institution with any other party for performing all or any portion of the specific project identified in this Agreement without the advance written consent of the U.S. Collaborating Institution.

M. PROJECT OFFICER AND PROJECT COLLABORATOR

1. The Indian Project Officer designated in this Agreement will be in active direction of the project and responsible for its administration on the part of the Indian Collaborating Institution. Changes or substitutions of Indian Project Officer will be made only with the concurrence of the U.S. Collaborating Institution.

2. The U.S. Collaborating Institution may designate a U.S. Project Collaborator who will have the responsibility on behalf of the U.S. Department of Health and Human Services for maintaining liaison with the Indian Project Officer.

N. PROTECTION OF HUMAN SUBJECTS

The Indian Collaborating Institution assures the U.S. Collaborating Institution that all research and demonstration involving human subjects which are conducted under this Agreement shall be in subject to review and approval by an Institutional Review Board in accordance with 45 CFR 46 (HHS Regulations for Protection of Human Subjects) to ensure that the

NEW DELHI

October 11, 1985

Dr. S. Ramachandran
Advisor
Dept. of Science & Technology
Technology Bhawan
New Mehrauli Road
New Delhi

Prof. V. Ramalingaswami
Director General
Indian Council of Medical
Research
Ansari Nagar
New Delhi

Dear Ram and Rama:

I have been asked to transmit to you a proposal for an agreement between the PHS Centers for Disease Control and the ICMR Tuberculosis Research Center for development of a Vaccine-Preventable Disease Study Center as a component of the Inco-US Vaccine Action Program. If you agree, the U.S. side would like to proceed with the development of this part of VAP as soon as possible.

As a next step in development of this activity, again if agreeable to you, the US side proposes an early visit by Dr. Steven Wassilak and/or Dr. Roger Bernier of CDC. It would be appreciated if an Indian counterpart could be named at an early date for the purpose of these discussions and for the development of a final proposal.

The Centers for Disease Control has tentatively allocated Rs. 11,400,00 for this project, including Rs. 10,000,000 for performance of research by the Indian collaborating institution and Rs. 1,400,000 for international travel.

I look forward to receiving your response on this proposal.

With best regards,

Sincerely,

Philip E. Schambra, Ph.D
Science Attache

~~XXXX~~

cc: Mr. Owen Cylke
Dr. Rogers Beasley
Dr. Tom Nicastro
Dr. George Curlin
Ms. Linda Vogel

PEs:11111

ANNEX-VI

DRAFT

**MEMORANDUM OF UNDERSTANDING FOR
THE VACCINE ACTION PROGRAM**

MEMORANDUM OF UNDERSTANDING
BETWEEN
THE GOVERNMENT OF THE UNITED STATES OF AMERICA
AND THE
GOVERNMENT OF THE REPUBLIC OF INDIA

FOR IMPLEMENTATION OF THE INDO-U.S. VACCINE ACTION PROGRAM

On June 16, 1985, the President of the United States Ronald Reagan and the Prime Minister of India Rajiv Gandhi, during the latter's state visit to the United States, announced the initiation of a new program to bring together U.S. and Indian scientists to jointly develop and test new and improved vaccines for immunization against diseases and to focus upon vaccine production, quality control and delivery methodology. This new effort has come to be called the Indo-U.S. Vaccine Action Program (VAP).

The announcement of the VAP is an important recognition that vaccines are among the most cost-effective of health technologies, and their widespread use in both countries is key to controlling the burden of vaccine-preventable diseases. With increasing attention throughout the world in health programs which promote child survival, there is a resurgence of interest in attacking this important category of diseases across the full spectrum of scientific, medical and public health disciplines. The strong program of cooperation in the health sciences between the two countries, notably the Reagan-Gandhi Science and Technology Initiative (STI), coupled with recent significant advances in research technology, provide a strong basis for the Vaccine Action Program.

The purpose of this Memorandum of Understanding (MOU) is to provide the framework for the implementation of the VAP. It defines the scope of the VAP, identifies the governmental participants in the VAP, establishes a joint management mechanism, and provides guidelines and procedures for such issues as patents and publications and protection of human subjects.

ARTICLE I

Governmental Participants

It is recognized that the nature of the cooperation dictates the participation by several governmental entities in both countries. The following listing identifies the principal Federal Government bodies on both sides which will be involved:

U.S. Participants

The U.S. Department of Health and Human Services

The U.S. Agency for International Development

Indian Participants

The Department of Science and Technology

The Ministry of Health and Family Welfare

The Indian Council of Medical Research

The Council for Scientific and Industrial Research

In addition to the principal governmental organizations identified above, it is understood that there will be numerous other participants. These include research institutions in both the public and private sector, State governments, and other agencies as may be identified for participation by the respective governments.

Both Governments recognize the complexity of managing and coordinating a program having many projects and participants. Thus, it is agreed that each Government will take steps to assure the establishment of an effective system to review and approve proposed joint activities, to assure effective implementation of program activities and to review and assess progress under the Vaccine Action Program.

ARTICLE II

SCOPE OF THE VAP

It is agreed that the Vaccine Action Program will encompass cooperation across the entire spectrum of vaccine-related technology, including research to develop new and improved vaccines and vaccine-related diagnostic methodology, vaccine field trials, vaccine production and quality control; and vaccine delivery methodology.

It is agreed that the following program activities will be part of the VAP:

1. Basic Research to Develop New and Improved Vaccines, including:

- A. Collaborative research and development projects targeted on high-priority vaccines which can be developed or adapted to the Indian situation within a reasonable period of time and applied in national immunization programs.
- B. Basic research leading to development of prototype vaccines for diseases of mutual interest, but for which insufficient research has been carried out.
- II. Development of rapid diagnostic technology to support essential epidemiological studies and to further health planning efforts.
- III. Clinical and Population-based Research to provide accurate descriptions of vaccine efficacy, diagnostic technology sensitivity and specificity, and safety of vaccines and immunization programs.
- IV. Vaccine Production and Quality Control to increase production capacity in India and to assure that vaccines are safe and efficacious.
- V. Immunization Service Delivery and Methodology, including operations research, to assure greater coverage of populations and reduce the burden of disease.

ARTICLE III

Planning and Coordination Mechanisms

A. Establishment of Joint Working Group

An Indo-U.S. Joint Working Group on the Vaccine Action Program will be established. The Working Group will meet in connection with the periodic Indo-U.S. Science and Technology Subcommission Meetings or at such other times as may be deemed appropriate and necessary by both Governments. The Working Group will report annually on progress of the VAP to the Co-chairs of the Indo-U.S. Science and Technology Subcommission.

The Joint Working Group will consist of representatives of each of the organizations identified in Article I and other Governmental officials as may be deemed necessary and appropriate. Each side will designate a ranking official to co-chair the Working Group, with the names of the co-chairmen to be communicated within 30 days of the signing of this agreement.

The Joint Working Group will:

- o Review program plans and recommend new areas of cooperation, based on recommendations from technical workshops and collaborating scientists.
- o Recommend measures to both Governments to assure that the program operates smoothly.
- o Address issues requiring joint resolution and which cannot be addressed effectively by the Executive Agencies (Secretariats).
- o Assure that efforts under the VAP do not conflict with or duplicate any other U.S.-Indo scientific collaboration.
- o Establish and communicate guidelines and criteria for selection of projects for inclusion in the VAP. As an initial step, it is agreed that a Joint Meeting on Vaccine Development Priorities will be convened in India in early 1986.

B. Establishment of Executive Agencies (Secretariats)

In order to assure that the VAP operates smoothly between Working Group Meetings and to help sustain the collegial nature of the joint program, each side will designate an Executive Agency (Secretariat).

Responsibilities of the Executive Agencies (Secretariats):

- o Be responsive to the Joint Working Group in assuring that the VAP operates as directed by the policies and guidelines set forth by the Joint Working Group.
- o Take necessary and appropriate actions, in cooperation with other participating agencies on their respective sides, to facilitate implementation of the VAP.
- o Collect information (such as evaluations and progress reports prepared in connection with specific activities) in order to assist the Joint working Group with its responsibility of assessing progress of the VAP and in preparation of the annual report on VAP.

- o Serve as a clearinghouse for ideas and recommendations for activities/projects under the VAP, assuring that these are presented to appropriate authorities and the VAP program leadership.
- o Maintain an information network in order to keep other parties engaged in scientific cooperation with India informed and to assure that there is no conflict or duplication with other Indo-US collaborative activities, including the Reagan-Gandhi Science and Technology Initiative, which was begun in 1982.

ARTICLE IV

FINANCING

Both Governments recognize that there will be no single source of funding on either side for the Vaccine Action Program.

Because of the multiplicity of sources of funding, it is agreed that the funding for each program or activity within the VAP will be agreed upon on a case-by-case basis.

It is recognized that, while the total program is based on mutual benefit and interest, there will be a number of activities, which are designed principally to benefit India or in which Indian scientists and institutions benefit more directly than do the cooperating U.S. institutions. In such cases, when U.S. AID development assistance is a funding source, it is agreed that these U.S. funds can be used to pay appropriate costs in the United States.

ARTICLE V

PROTECTION OF HUMAN SUBJECTS

Both Governments recognize the importance of the protection of human subjects in any medical program. In recognition of this, both India and United States have adopted laws and regulations on the protection of human subjects. It is agreed that, for the Vaccine Action Program, a joint Assurance of Protection of the Rights and Welfare of Human Subjects of Research in the Indo-U.S. Vaccine Action Program, which is acceptable to both Governments, is established. This Assurance will become Ann.

ARTICLE VI

PATENTS AND PUBLICATIONS

It is recognized that the work carried out under the VAP may result in patentable results and in the publication of the scientific findings. In order to assure that the rights of both countries are protected, an accord on Patents and Publications will be developed and become Annex 2 to this MOU

As a principle, it is agreed that scientists on both sides will be encouraged to publish, both jointly and as individuals, their findings. In any publication, an appropriate reference will be made to the Indo-U.S. Vaccine Action Program.

ARTICLE VII

BIOTECHNOLOGY

It is recognized that some of the medical research, such as in the production of antigens, carried out under this agreement will involve Recombinant DNA technology.

Whereas both countries have similar regulations governing the conduct of Recombinant DNA research, it is agreed that all research, involving Recombinant DNA technology, will be carried out in accordance with the laws and regulations of the country in which the research is conducted.

ARTICLE VIII

EXCHANGE OF DATA, SPECIMENS, MATERIALS AND EQUIPMENT

Both parties agree that the exchange of technical information, specimens, materials and equipment will be fostered. Toward this end, both Parties agree as follows:

- o To facilitate access to collaboratively developed information under the VAP. This includes the exchange of data, reports and other appropriate documents.

- o Facilitate customs clearance for bacterial and viral strains, reagents, samples for laboratory study, and other perishable products.
- o Facilitate duty-free clearance of equipment and supply shipments.

ARTICLE IX

EXCHANGE OF PERSONNEL

It is recognized that at the VAP will involve numerous exchanges of administrative and scientific personnel throughout each year. In many cases, rapid clearance, both by the sending country and the receiving country, must be assured.

Both Governments agree to provide the necessary clearances (exit permission by the sending country and visa issuance by the receiving country) on a priority basis, subject to their respective laws and regulations.

ARTICLE X

ENTRY INTO FORCE AND TERMINATION

This memorandum of Understanding shall enter into force on the date of signature and shall remain in force for five years, after which it may be renewed by both parties by written agreement.

Done of the day of

For the Government of the
United States of America:

For the Government of the
Republic of India:

Ambassador

ANNEX-VII

BIBLIOGRAPHY

BIBLIOGRAPHY

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