

ADVANCES IN **Biopharmaceutical Technology in**

India

Eric S. Langer, Editor



**Society for Industrial Microbiology
BioPlan Associates, Inc.**

Advances in Biopharmaceutical Technology in India

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Editor: Eric S. Langer



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Eric S. Langer
Managing Editor

Preface

This study was undertaken, managed and coordinated by BioPlan Associates, Inc., a biopharmaceutical management and marketing research consulting firm in Rockville, MD, based on nearly 20 years experience and knowledge of the market segment. BioPlan surveyed the industry to identify required content, and then selected subject matter experts to author relevant chapters to this study.

The Society for Industrial Microbiology (SIM), in recognizing the importance of applied sciences in biotechnology processes, has lent its name to this endeavor. The Society for Industrial Microbiology is a nonprofit professional association dedicated to the advancement of microbiological sciences, especially as they apply to industrial products, biotechnology, materials, and processes. Founded in 1949, SIM promotes the exchange of scientific information through its meetings and publications, and serves as liaison among the specialized fields of microbiology. Membership in the Society is extended to all scientists in the general field of microbiology.

India is one of the fastest growing economies in the world. The country has invested heavily in advancing its pharmaceutical and biopharmaceutical technologies to improve its healthcare systems, its population's general health, and its overall economy.

Both scientists and entrepreneurs in India have made important contributions to advancing the field at many levels. This study provides a framework from which both those new to India's rapid advancements in biotherapeutics and vaccines, and those with long histories can recognize the potential, and plan for the future. The findings of this study support worldwide public health and economic policy.

Each chapter provides unbiased, peer-reviewed perspectives of the current state of the science and technology associated with biopharmaceuticals in India. While no single work can encompass all the advances being made in the field, this study offers a comprehensive assessment of the technological and economic advancements in India.

The intended audiences include decision-makers at biopharmaceutical research organizations, biotherapeutic manufacturers, contract manufacturing organizations, suppliers to the industry, policy-makers, and international entities evaluating this market. We plan to keep this study current by providing regular updates as technologies, and the industry advance.

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Biopharmaceutical Research Collaborations between India and the West: A Guide to Prospective Partnerships

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ABSTRACT

Biopharmaceutical research, and in particular development of innovative drugs and vaccines require concentrated efforts on many levels, as well as multiple skills and expertise. Research collaborations between two or more life science organizations are therefore common in the biopharmaceutical industry. Increasingly these collaborations can involve organizations from different countries and different continents, and in particular they now include partnerships between the public and the private sectors. The recent changes in Indian patent law and its policies in response to the requirements of the Trade-Related Aspects of Intellectual Property (TRIPS), and the recent shift in India to a more innovation-intense pharmaceutical industry, as well as the immense progress in India's infrastructure and capacity for basic research in the biomedical field have all made India's life-science organizations attractive collaborators to their western counterparts. These collaborations have been further facilitated by the many Indian life-science returnees who have established links in the West.

This chapter is intended to serve as a guide to prospective collaborators in both India and the West. Its first half outlines the factors that have made the India's biopharmaceutical industry an attractive collaborator to its western counterparts, a fact that resulted in India's emergence as a hub for international R&D, manufacturing and clinical trials. The second half of the chapter starts with the history and the chronology of U.S.-India collaboration in science, highlighting the areas of health care and biomedical research, and goes on to provide information regarding the different programs for collaborative initiatives that are available from the U.S. Department of Health and Human Services (HHS) and its agencies such as the National Institutes of Health (NIH), its licensing arm, the Office of Technology Transfer (OTT), and the Center of Disease Control and Prevention (CDC). On the Indian side the chapter highlights the contributions to such collaborations of the Indian Department of Biotechnology (DBT) under the Ministry of Science and Technology. DBT

works in concert with its U.S. counterparts to continually support a large variety of programs, and to form new research initiatives. These joint U.S.-India efforts fund research, and support training, bilateral meetings and conferences, as well as facilitate open exchange of scientific information between the two countries.

The chapter provides websites of the different programs as well as of the institutions in the U.S. and in India who currently benefit from the resources and programs described in the chapter. It is hoped that the information provided in the chapter will be utilized by scientists on both sides of the ocean to establish new and innovative partnerships for the benefit of global public health.

Biopharmaceutical Research Collaborations between India and the West: A Guide to Prospective Partnerships

A. Introduction to Life Science Research in India

Since independence in 1947, India has seen an important role for scientific and technical collaborations and the benefits that they can provide in the quality of human life. Indeed Prime Minister Nehru has been quoted as saying that “the future belongs to science and those who make friends with science.” Over the past sixty years this has resulted in policies in the country that focused on developing education and infrastructure resulting today in a strong science and technology capacity. This strong science and English language base provide life science organizations in India with capabilities in biotechnology, agriculture, information technology and pharmaceuticals that are ideal for collaborative projects with western organizations.

Life science organizations in India with their large and highly skilled scientific and technical workforce, less expensive R&D, manufacturing and information technology skills, access to advantageous governmental policies backed by a growing entrepreneurial culture have a promising future that is only now beginning to be utilized by outside groups. Interest by Indian academic and business life science organizations to collaborate with their western counterparts, and conversely, the interest of western life science organizations to partner with their Indian counterparts has been increasing of the years as both sides start to recognize the emerging opportunities and synergisms that are possible from working together.

This chapter will provide an overview for western scientists and business people who are looking to cooperate with India’s increasingly sophisticated bioscience organizations in order to expand their activities in India and to establish R&D, commercialization, manufacturing operations and partnerships as well as just for basic research projects. The importance of this cannot be underestimated since in this current era of biopharmaceutical development companies must collaborate with public and academic institutions wherever in the world where basic research, early discoveries or later development are being made in order to optimize research and product commercialization.

These U.S.-India collaborative efforts fund joint research projects, and support training, bilateral meetings and conferences, as well as facilitate open exchange of scientific information between the two countries.

To set the stage for this, the chapter starts with a description and discussion of the status of the biopharmaceutical industry in India and its prospective growth. Existing collaborations of Indian private enterprises with their western counterparts are explained and how the existing capacities of these Indian firms are being used for collaborations for biogeneric and biopharmaceutical development.

Following the examples of industrial collaborations, academic collaborations between the United States and India will be shown – inspired by the many bilateral agreements between the two governments and implemented by the appropriate government agencies (the National Institutes of Health (NIH) and the Center for Disease Control and Prevention (CDC) in the U.S. and the Department of Biotechnology (DBT) in India).

Because of their long history and extensive focus in the life sciences area, these bilateral collaborations are particularly good examples for prospective collaborators both in the U.S. and India of the type and breadth of interactions that are possible between U.S. and Indian life science organizations. Beginning with the history and the chronology of U.S.-India collaboration in science, this section highlights the areas of joint health care and research, and goes on to provide information regarding the different programs for collaborative initiatives that are available from the U.S. Department of Health and Human Services (HHS) and its agencies such as the National Institutes of Health, its licensing arm, the Office of Technology Transfer (OTT), and the Center of Disease Control and Prevention (CDC).

On the Indian side, the chapter illustrates the contributions to such collaborations of the Indian Department of Biotechnology under the Indian's Ministry of Science and Technology. DBT works in concert with its U.S. counterparts to continually support a large variety of programs, and to form new initiatives related to life sciences and biopharmaceuticals. These include work in such areas as tuberculosis, vaccines, HIV/AIDS, waterborne disease and involve a number of useful mechanisms relevant for collaborations such as contracts, grants, formal and informal joint research efforts as well as technology licensing. Of particular note is a case study relating to rotavirus vaccine development license by four Indian institutions from the National Institutes of Health.

These U.S.-India collaborative efforts fund joint research projects, and support training, bilateral meetings and conferences, as well as facilitate open exchange of scientific information between the two countries. Through these various examples and information references provided, it should be possible to improve and enhance the number of collaborative research and development efforts between western research organization and their counterparts in India for the benefit of global public health.

B. India – An Emerging Hub for International Collaborations in Biopharmaceutical Technologies

With approximately 200 companies, the biotechnology sector in India has witnessed accelerated growth in recent years that make it ripe for collaboration and joint development projects. The country's biotechnology sector grew by 39% to reach a value of \$705 million in 2003-2004, with biopharmaceuticals sector occupying the largest market share of 76%, followed by bio-agriculture 8.42%, bioservices 7.70%, industrial products 5.50% and bioinformatics 2.45%. The Union Science and Technology Minister, Kapil Sibal, released a draft National Biotechnology Development Strategy in March 2005 that envisions the biotechnology sector to grow still further to reach a value of \$5 billion by 2010.

With the advent of the new product patent policy in January 2005, Indian pharmaceutical companies are undergoing substantial transformation. Challenges of globalization and the introduction of a new product patent regime have motivated the Indian industry to gradually shift focus onto more research intensive, innovative bio-pharmaceutical products by expansion of their international generic business, contract manufacturing services, contract research services, and research and development (R&D) capabilities. International pharmaceutical and biotech companies, which stayed away from pre-2005 hostile IP regime, are exploring ways to leverage the full benefits of India's unique set of skills, resources, capabilities and opportunities. India's rapidly improving skill set in drug discovery and development research, and improving government policies supportive of foreign direct investment and participation has created substantial strategic opportunities for Western pharmaceutical companies. Indian companies are now rapidly growing from biotech outsourcing hub for low-IP sensitive discovery, custom synthesis, process synthesis, and clinical trials to emerging as collaborative R&D partners offering high-value services. According to a recent survey by Cambridge Healthtech Associates (CHA) entitled *Globalization of Drug development: India, June 2006*, over three-quarters of the top 50 Western pharmaceutical companies are conducting drug development activities in India – more than in any other emerging country.

1. R & D in India

Pharma companies globally are investing heavily in research and development (R&D) to develop new drugs. According to a report by Pharmaceutical Research and Manufacturers of America (PhRMA), the U.S. biotech and bio-pharma investment in R&D was \$38.8 billion in 2004, a 12.6% increase from \$34.5 billion in 2003. This increase in pharma R&D investment in 2004 is about five times higher than that in 1990 and about twenty times higher than that in 1980. Out of the \$38.8 billion that the U.S. pharmaceutical industry invested in R&D in 2004, around 21% was spent

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Ranbaxy, which boasts of having the industry's largest R&D budget, had an R&D spending level of over 7% of sales in 2005 compared to just 6% in 2004.

on outsourcing. With the reported cost of developing a new drug soaring enormously over the years from \$100 million in the 1980s to more than \$800 million now, pharmaceutical companies in the U.S. and Europe are under immense pressure to cut R&D costs.

India is rapidly emerging as an R&D hotspot that can offer an attractive destination where companies can tap into an existing large pool of inexpensive scientific and technical workers with good links to academic research facilities, and provides an environment where innovation is supported by the introduction of product patents regime. According to Mr. Utkarsh Palnitkar, Director and Head of Life Sciences Practice, Ernst & Young India, the cost of doing R&D and introducing a new molecule in India is 30-40% lower than the cost involved in a developed country.

The new product patent regime has introduced a fresh vigor into the country's drug discovery research. Indian pharmaceutical companies are significantly increasing their R&D spending. For example, Ranbaxy views its R&D capabilities as a vital component of its business strategy that will provide the company with a sustainable, long-term competitive advantage. The company today has a pool of 1,100 scientists who are engaged in path-breaking research. Ranbaxy, which boasts of having the industry's largest R&D budget, had an R&D spending level of over 7% of sales in 2005 compared to just 6% in 2004. The company plans to progressively increase its investment in R&D to 9%-10% of sales by 2007. Other examples are Nicholas Piramal spending 5% share of its total sales on research in 2005-06 compared with 3.5% in 2004-05 and Sun Pharma's R&D spending of 9% of the company's total sales in 2005-06, compared to just 8% in 2004-05.

2. Existing or Emerging Focus Areas for Indian Biotech and Pharmaceutical Companies

Contract or Collaborative Research

Most Indian biotech companies have opted for contract or collaborative research as a service model at their start-up stage in order to earn early revenues. Syngene, Aurigene, Genotypic Technology, Chembiotek, Cytogenomics and Metahelix are some examples of such service based biotech companies, while companies like Avesthagen and Bangalore Genei have opted for contract research services as a secondary business to generate revenues to support existing business lines. According to a CHA report (*Globalization of Drug development: India, June 2006*), services companies such as GVK Biosciences, Sai Life Sciences, Chembiotek, Syngene, Avra, and others have thrived with growth now moderating to the 50%-70% range. Many of these companies have to date provided only a limited range of services such as low-IP sensitive discovery services, process R&D, and custom synthesis. These companies are now aggressively investing in high-value R&D capabilities and harbor ambitions of original R&D once they reach a certain profit level.

Syngene, a R&D subsidiary of India's top biotech company Biocon, in 2004 entered into a three-year contract research agreement with the Novartis Institutes for Biomedical Research, Inc. for carrying out research projects to support new drug discovery and development, primarily in the early stages and involving small molecules in oncology and cardiovascular segments.

Avesthagen, a healthcare technology group focused on the convergence between pharmaceuticals, food and preventive personalized medicine, is based on a collaborative research model. Avesthagen's business model is to combine IP & product development for long term sustainable revenue generation and value addition, with R&D services and collaborative research programs for/with other parties to generate an early revenue stream and market focus. In 2005 Avesthagen established multiple joint ventures with international as well as Indian partners. Avesthagen formed alliances with AstraZeneca (genomics and metabolomics for infectious diseases), Novartis (molecular biology), BioMérieux (cancers, emerging pathogens and infectious diseases diagnostics), Nestle and Itochu (nutraceuticals), University of Minnesota (obesity control), Netherlands Organization for Applied Scientific Research - TNO (nutrigenomics), Centre for Clinical & Basic Research-CCBR (diagnostics and nutraceuticals), Cipla (biopharmaceuticals), and Imperial College London and Cambridge University (population genetics study and infectious diseases programs).

Clinical Research Organizations

Clinical research is currently in the news for its immense business potential in India with the focus of clinical research outsourcing to India shifting from cost advantages to quality in conducting clinical trials and data management services, and rapid response (see Table 1). A number of contract research organizations (CROs), encouraged by the recent regulatory reforms, are setting up operations in India.

The broadly developed information technology infrastructure in India provides added advantage to ensure speedy conduct of studies and flow of information/data from the clinical sites to the sponsors' databases. Experts believe that with the new patent regime, India will soon make a mark for itself in the area of clinical research. The total market value of clinical research performed in India in 2001-02 was about \$70-80 million. The Confederation of Indian Industry predicts that it will grow to \$200 million by 2007 and anywhere between \$500 million and \$1 billion by 2010.

The pace for drug trials in the country is so fast that the Clinical Data Interchange Standards Consortium (CDISC), USA, a non-profit organization committed to the development of clinical research organizations' standards the world over, is planning to form an India-CDISC Coordinating Committee on the lines of Europe CDISC Coordinating Committee (ECCC) and Japan CDISC Coordinating Committee (JCCC).

The Confederation of Indian Industry predicts that it will grow to \$200 million by 2007 and anywhere between \$500 million and \$1 billion by 2010.

Table 1. Benefits of conducting clinical trials in India

- Low-operational costs, 30-40% lower than the cost involved in a developed country.
 - A large pool of treatment naïve patients with multiethnic and multiracial backgrounds.
 - Rapid patient enrollment rate- 0.3 patients per month in U.S. as against 3 patients in India during the same period.
 - Vast pool of scientific talent, well-trained and enthusiastic investigators.
 - Wide spectrum of disease profiles.
 - Robust healthcare infrastructure, such as nearly 700,000 specialty hospital beds, 221 medical colleges.
 - Robust information technology infrastructure ensures efficient clinical data management, speedy conduct of studies and flow of clinical data.
 - Highest number of U.S. FDA approved plants outside U.S.
 - Established bulk-drug and formulation industry.
 - Well-trained medical community to global standards and increasing awareness of Good Clinical Practice.
 - English as the primary business and medical language.
 - New laws encouraging more Foreign Direct Investments in India.
 - Government commitment to provide Intellectual Property Protection.
 - Changes in regulatory policies to facilitate clinical research.
-

With a population of more than 1.1 billion, India offers a large pool of treatment naïve patients with multiethnic and multiracial backgrounds. This, combined with India's highly qualified work force and numerous world-class medical facilities that meet the global requirements for clinical testing, offers a strong infrastructure for human clinical testing. India has a large pool of highly trained physicians, nurses, and technical personnel consisting of BS, MS, Ph.D.-level workers. In 2005, approximately 600,000 doctors were registered with state medical councils in India, of which about 30% held specialist qualifications. Additionally, many highly educated Indians that had earlier immigrated to the U.S. and Europe are now returning home to participate in the rapid modernization of their country. Currently, over 80 government and privately owned hospitals are actively engaged in clinical trials. With more than 14,000 hospitals in the country and a total bed capacity of nearly 900,000, hospitals engaged in clinical trials are expected to grow each year. However, many public hospitals will require infrastructure improvements before they can effectively participate in clinical trial programs.

The Indian government has been actively contributing to help capture outsourcing opportunities for clinical trials. The Indian government has recently amended Schedule-Y of the Drugs and Cosmetics Rules to allow clinical trials to be carried out in India concurrently with other global trials by removing the "phase-lag" condition between India and the rest of the world in clinical trials of new drug substances.

Some have raised fears that Indian patients may be treated like “guinea pigs”. The low literacy levels of many poor patients and volunteers, raises concerns of adequate informed consent about the clinical trials risks. The Indian government has recognized the need for regulatory policing that ensures protection of human subjects on clinical trials. The Drugs Controller General of India (DCGI) — the equivalent of the U.S. Food and Drug Administration (FDA) has streamlined the provisions for conducting clinical trials in the country in accordance with the International Conference on Harmonization (ICH) good clinical practice (GCP)/good laboratory practice (GLP) guidelines and FDA standards. All medical facilities have been mandated to meet the GCP procedures. The Indian Government along with the World Health Organization (WHO) has undertaken a massive campaign to provide training support to medical and regulatory personnel necessary to achieve this goal. The Indian Government is also planning to introduce draft guidelines on ethical and patient safety issues in different fields like stem cell research, genetically modified food, genetically modified drugs, biomedical and behavioral research on HIV/AIDS, assisted reproductive techniques, and gene therapy. In addition, India has provided exemptions for import duties on clinical trials products and eliminated the procedural hurdles that were prevalent in the past. To provide a financial incentive for drug developers to outsource their R&D work to India, the Indian government has instituted ten-year tax holiday concessions on income arising from R&D spending and intellectual property alignment with the World Trade Organization guidelines.

Many major pharmaceutical companies have already successfully used clinical trials’ data from India for US FDA New Drug Application (NDA) submissions. Today global pharma companies like GlaxoSmithKline, Johnson & Johnson, Eli Lilly, AstraZeneca, Novo Nordisk, Aventis, Novartis, Sanofi-Aventis, Merck, Wyeth, Bristol-Myers Squibb, Roche and Pfizer are included in the list of companies conducting clinical research trials across various Indian cities. GlaxoSmithKline is currently carrying out the largest number of clinical trials in India. Pfizer has invested an estimated \$13 million in trials since 1995 to treat malaria, osteoporosis, breast cancer and schizophrenia. Many multinational CROs have also outlined plans to tap India’s large pool of patients.

U.S.-based Quintiles Transnational, the first global CRO to establish a presence in India, has had tremendous success recruiting patients quickly and efficiently. Since its incorporation in India in 1997 it has conducted more than 100 clinical studies involving over 700 sites and nearly 15,000 patients in a range of therapeutic areas including oncology, infectious diseases, gastroenterology, neurology and cardiovascular disease. SIRO Clinpharm, Clinigene (subsidiary of Biocon), Wellquest (clinical trials division of the Nicholas Piramal Group) are some of the local companies that are building their reputation as specialists in clinical research.

India has provided exemptions for import duties on clinical trials products and eliminated the procedural hurdles that were prevalent in the past.

Contract Manufacturing Organizations

Manufacturing was among the earliest activities to be outsourced by global pharmaceutical majors to India. Over the last decade India has emerged as a major source of active pharmaceutical ingredients (APIs) for global pharmaceutical companies. Today India has the maximum number of U.S. FDA-approved plants outside the U.S. and Indian companies are the largest submitters of Drug Master Files (DMFs) outside the U.S. (see Table 2 below). India’s technical talent in process development, cGMP manufacturing drugs and vaccines to U.S. FDA and EU standards and the introduction of product patent regime since 2005 has played a key role in India’s emergence as a globally preferred destination for outsourced manufacturing in pharmaceuticals.

Table 2. Active Drug Master Files submitted in 2006

Countries outside US	Type 2*	Type 3*	Type 4*	Type 5*
India	308	23	8	0
China	101	5	0	0
Italy	44	8	0	0
Germany	24	14	6	0
Spain	17	1	6	0
Israel	17	0	0	0
Japan	15	10	13	1
Canada	11	9	1	0
France	10	13	1	0
Switzerland	10	3	0	0
Taiwan	9	0	3	0
Mexico	8	9	0	0
Hungary	6	0	0	0
UK	6	9	1	0
Czech	5	0	0	0
Netherland	5	2	0	2
Denmark	4	1	0	0
Belgium	3	0	0	0
Austria	3	2	0	1
Finland	2	0	0	0
Sweden	2	4	0	0
Australia	1	1	0	0
S. Africa	0	0	0	0
Turkey	0	0	2	0
U.S. and rest of world	91	61	38	6
Total active DMF	702	175	79	10
India %	43.9	13.1	10.1	0.0

Note: Type I Manufacturing Site, Facilities, Operating Procedures, and Personnel is no longer applicable

- Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
- Type III: Packaging Material
- Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
- Type V: FDA Accepted Reference Information

While the larger Indian pharmaceutical companies started focusing on new drug discovery and generic exports during mid-1990s to set off the imminent challenges posed by the product patent regime of not being able to manufacture and sell patented products, contract manufacturing became a more viable business model for several small-medium sized Indian companies.

Companies offering contract-manufacturing services in India are finding opportunities in both on and off-patent molecules. Several Indian companies such as Nicholas Piramal, Biocon, Dishman Pharma, Shasun Chemicals & Drugs, Jubilant Organosys, Divi's and Matrix have agreements with global generic companies for off-patent molecules. Cadila Healthcare and Altana AG set up a joint venture in 1998 to manufacture and supply two intermediates for Altana's blockbuster product *Protonix* (pantoprazole). Protonix is a gastrointestinal drug with global sales in excess of \$2 billion. The product is under patent till 2010 in U.S. and till 2016 in Europe. U.S. biosciences company Codexis had established collaboration with India-based Matrix Laboratories in 2005, for the development and commercialization of an API for a high-value pharmaceutical product. Codexis will use its proprietary pharmaceutical process re-engineering technology platform to develop a novel synthetic process for the product. The process will be then transferred to Matrix for scale-up and manufacturing. Under the terms of the agreement, while Codexis will receive R&D funding, milestone payments and a royalty on net sales of the product, Matrix will gain exclusive manufacturing and marketing rights to the novel process.

A large number of multinational companies including Pfizer, Bayer, GSK, Aventis, Merck, and Novartis are today relying on production facilities and pharmaceutical companies in India to meet their requirements for APIs and intermediates. Of the twenty global pharmaceutical companies, fifteen have an active presence in India. Several international pharma companies, including Teva, Sandoz, Pliva and Ratiopharm, also have acquired or set up their own manufacturing facilities in India. Teva of Israel made an entry into the Indian market in 2003 by acquiring JK Industries' pharmaceuticals business. Teva had since launched a fully-owned subsidiary R&D center in India, Regent Drugs Ltd, focused on process development for APIs and advanced intermediates of APIs. In January 2006, Teva acquired the U.S.-based Ivax to become the world's biggest producer of generic drugs. Sandoz, Teva's biggest competitor and the generics arm of Novartis, has recently set up its third manufacturing plant in India. In August 2006, U.S. generic drug maker Mylan decided to spend around \$736M to acquire a controlling stake in

A landmark agreement in 2003 between India's largest pharmaceutical company, Ranbaxy and world's second largest pharma corporation, GlaxoSmithKline Plc ... marks the beginning of a new phase in the pharmaceutical research in India.

Matrix Laboratories, an Indian manufacturer of APIs in order to expand its manufacturing platform.

Funding by Venture Capitalists

According to Ernst & Young global biotech report 2006, the Indian biotech sector is gaining investor confidence. The sector has not only attracted funds from international organizations like the World Bank, but now Indian biotech companies are successfully tapping investors and hedge funds for cash.

Venture funds, which until now have rarely invested in Indian pharmaceutical companies, are now increasingly participating in the innovative R&D efforts of Indian firms. GangaGen, Inc., which has operations in Bangalore, India and Ontario, Canada, has raised \$3.9 million primarily from U.S. investors, including U.S.-based ICF Ventures that specialize in Indian investments.

In March 2006, Dr Reddy's Laboratories entered into a deal with Citigroup Venture and ICICI Venture Funds to form an integrated drug development company called Perlecan Pharma Private Limited with an equity capital commitment of \$52.5 million. In this deal Dr. Reddy's has transferred to Perlecan all rights and titles for the development and commercialization of four discovery molecules.

Partnership Arrangements

Partnership arrangements, marketing alliances/licensing deals, joint ventures between Indian bio-pharmaceutical companies and their international counterparts are increasingly developing. The increasing confidence due to introduction of the product patent regime has made such alliances more attractive. While primary reasons for international companies to partner with Indian companies will be to reduce the cost and cycle times of product development, the partnering model is driven by India's need for a two-way flow of benefits. Foreign companies can provide the knowledge that Indian companies lack such as essential know-how about discovering, obtaining regulatory approval for, and marketing new drugs (BioCentury, The Bernstein Report on Biobusiness, 2004, Vol. 12, No. 34). Indian companies acknowledge that though they have expertise in bioinformatics, lead optimization, preclinical development, scaling up, and manufacturing, they lack the resources and expertise in lead generation, toxicology studies, regulatory affairs and patenting.

A landmark agreement in 2003 between India's largest pharmaceutical company, Ranbaxy and world's second largest pharma corporation, GlaxoSmithKline Plc in the area of drug discovery and clinical development marks the beginning of a new phase in the pharmaceutical research in India. The agreement is a clear and open recognition of research capability of Indian pharmaceutical industry. The R&D alliance will cover several therapeutic areas including urology, anti-fungal, anti-bacterial, diabetes, inflammation and asthma. While GSK will mostly provide the leads or potential molecules to be developed as drugs, Ranbaxy will undertake the initial research, development

and clinical works. Once a compound has been selected as a development candidate, in most cases, GSK will complete development. GSK will have the commercialization rights worldwide, while Ranbaxy will take the lead in India. Ranbaxy, with the consent of Glaxo may co-promote in EU and U.S.

This collaboration provides an avenue to Ranbaxy to leverage its discovery and early product development strengths and gain access to large database of drugs of GSK as well as cutting edge technologies for drug discovery while GSK benefits from Ranbaxy's early drug development strength to accelerate its internal drug discovery programs. Another outcome of Ranbaxy-GSK alliance is the emergence of a new relationship between India's research-based pharmaceutical companies and their counterparts in the U.S. and Europe.

In 2005, Dr. Reddy's Laboratories entered into a co-development and commercialization agreement with Denmark-based Rheoscience A/S for the joint development and commercialization of balaglitazone (DRF 2593) a partial PPAR-gamma agonist, for the treatment of type 2 diabetes. Under the terms of the agreement, Rheoscience will fund all the costs associated with the Phase III clinical trials of DRF 2593 and Dr. Reddy's will pay Rheoscience a pre-determined amount towards its share of the development costs. Rheoscience will retain the marketing rights in Europe and China and Dr. Reddy's will retain the marketing rights in the U.S. and the rest of the world. Furthermore, Rheoscience will obtain all necessary regulatory approvals on behalf of Dr. Reddy's in the United States.

U.S.-based Nobex Corporation entered global research collaboration with Biocon Ltd of India to accelerate its project to develop an oral formulation of insulin, to provide a more patient-friendly alternative to current injectable products for diabetes. In 2005, the two companies entered another collaboration to jointly develop an oral peptide product for the treatment of cardiovascular disease. Both the collaborations combine the proven peptide production capabilities of Biocon with the proprietary oral peptide-delivery technology of Nobex. In March 2006, Biocon acquired for \$3.5 million the intellectual property assets of its partner Nobex, which had filed for bankruptcy in the U.S.

Off-shore Acquisition

Analysts are observing that Indian pharmaceutical companies are in a merger & acquisition spree lately. The main aim of acquisitions of U.S. or European companies by the Indian companies have been to either boost their presence in those countries' markets or to establish a manufacturing or to expedite regulatory processing of their Abbreviated New Drug Applications (ANDAs). As the first pharma Indian company to go overseas, Ranbaxy Labs already has a strong presence in Europe. Ranbaxy already has a strong presence in UK and Germany and acquired France's RPG Aventis in 2004. Aiming to expand its presence in the EU market, Ranbaxy Labs in 2006 acquired Terapia (Romania's sixth largest generic player), Ethimed (Belgium's 10th largest generic

In March 2006, Biocon acquired for \$3.5 million the intellectual property assets of its partner Nobex, which had filed for bankruptcy in the U.S.

Currently, Indian companies lack the resources to carry the new chemical entities from start-to-finish, forcing them to often out-license molecules after taking them into either Phase I or II stages.

company), Mundogen (GSK's generic business in Spain) and Allen S.p.A. (GSK's generic business in Italy).

Dr Reddy's Lab, in its first overseas acquisition in 2002, acquired two small British generic drug companies – BMS Laboratories and its subsidiary Meridian Healthcare. With this acquisition, the pharma major ventured into the European market, which it was eyeing for some time. In 2004, Dr Reddy's Laboratories acquired access to drug delivery technology platforms in the Dermatology segment through the acquisition of U.S.-based Trigenesis Therapeutics. In 2005 Dr Reddy's acquired Roche's API Business at the state-of-the-art manufacturing site in Mexico with a total investment of \$59 million. Recently in March 2006, Dr Reddy's Labs' acquired a German generic firm Betapharm for 480-million Euro (\$570 million), in one of the biggest overseas acquisitions by an Indian pharma company. Betapharm is the fourth largest player in the German market, which is the largest generics market in the world after the U.S.

Some of the other smaller U.S. and European acquisitions by the Indian pharma industry during 2005 include Matrix Laboratories buying a controlling stake in Belgium's Docpharma and Switzerland's Explora Laboratories, Torrent Pharmaceuticals Ltd. acquiring Germany's Heumann Pharma, Jubilant Organosys acquiring U.S.-based Target Research Associates and Trinity Laboratories.

Out-licensing Arrangements

Currently, Indian companies lack the resources to carry the new chemical entities from start-to-finish, forcing them to often out-license molecules after taking them into either Phase I or II stages. Dr Reddy's Labs, Ranbaxy Labs, Torrent Pharma, and Glenmark Pharma have out-licensed some of their molecules to global pharma players. Such outlicensing deals, though offer both upfront and milestone-linked payments to Indian companies, have its own inherent risks. International pharmaceutical companies often take up 2-3 probable candidates for further development and Indian companies often have to wait for 3-4 years only to see it being dropped for various reasons, according to Dr. Anji Reddy, chairman, Dr Reddy Laboratories.

Dr Reddy's Laboratories' reshaped R&D strategy of out-licensing four of its molecules to Perlecan Pharmaceuticals at an early stage of development has altered the risk-reward equation of potential revenues from its drug pipeline, with Dr Reddy Laboratories initially holding a 14% stake and Citigroup and ICICI Ventures putting up the remaining venture capital funding. According to Dr. Reddy, once a common code on good clinical practices comes into effect in the country, and the infrastructure is standardized for the companies to conduct their own trials, Indian pharma companies focusing on research can stop out-licensing their molecules to multinational companies.

In-licensing Arrangements

In-licensing agreements are currently being undertaken in a big way by many Indian companies. This will ensure that the domestic pharmaceutical industry will also be benefited by way of newer molecules. With intellectual property rights in pharmaceuticals secured, Nicholas Piramal India Ltd (NPIL) has been able to interest overseas pharmaceutical majors to invest in India. It has several in-licensing and technology transfer agreements with leading multinational pharma companies, including Biogen Idec of the U.S. for marketing its anti multiple sclerosis drug Avonex and Amevive for psoriasis, U.S.-based Gilead Sciences Inc's biotech for marketing drug Ambisome for deep seated fungal infections in India, marketing of Italian company's Chiesi's lung surfactant drug Curosurf, French Pierre Fabre's dermo-cosmetic drugs Exomega and Kertyol, Genzyme Corporation of U.S. for marketing a viscose supplement Synvisc, Germany's Gruenthal for marketing a pain management drug Trimadol, and a technology transfer agreement with Ethypharm of France for paracetamol melt tablets drug delivery technology. Several other companies have since undertaken in-licensing agreements to acquire new technologies, including Ranbaxy and Zydus Cadilla.

A later section of this chapter entitled "Technology Transfer Activities between the NIH and India" is devoted to licensing arrangements between Indian's biotech companies and public academic institutions in the Unites States.

Prospects for the Future

The Indian pharmaceutical companies are rapidly attaining critical mass in terms of skills and capabilities to integrate fully with the global pharmaceutical sector. Today several Indian pharmaceutical companies are approved by U.S. FDA and are listed at NASDAQ. The development of several products, such as AIDS diagnostic kits, Hepatitis B vaccine, recombinant human insulin as well as other recombinant therapeutics with high quality but at substantially lower cost, demonstrates the potential of technology innovation in Indian pharma sector. Several R&D agreements, increasing clinical research activities, out-licensing and in-licensing arrangements, high profile offshore mergers and acquisitions by Indian companies, indicate the momentum gained by the Indian biotechnology and pharmaceutical industry. From the industry's perspective much of this is due to the country's introduction, on January 1, 2005, of a system of product patents. The Indian government is also moving forward with initiatives, policies, regulations and programs to boost R&D activities in India by both international and local pharmaceutical companies. Some of the recent proposals and initiatives by Indian government, as described in the draft National Biotechnology Development Strategy for 2005, include allowing 100 per cent Foreign Direct Investment, exemption from the requirement of compulsory licensing, promoting and supporting at least ten biotech parks by 2010, creating several technology transfer cells,

With intellectual property rights in pharmaceuticals secured, Nicholas Piramal India Ltd (NPIL) has been able to interest overseas pharmaceutical majors to invest in India.

introducing new grants and loans for promoting small business innovation research, encouraging collaborative research between the public and private sectors, establishing a center for translational research, and finally establishment of a National Biotechnology Regulatory Authority to provide for a faster and more efficient regulatory clearance. With respect to the latter, at the time of the writing of this chapter the Central government's plans to restructure the regulatory process in India have been disclosed,⁷⁸ and will be detailed in a separate section immediately following this section. Though most of the above-mentioned policies and proposals are yet to be implemented, they clearly encourage both international and Indian pharma and biotech companies to invest their resources in India.

Proposed Changes in the Regulatory Process-A positive Measure to Improve the Drug Industry

The Indian Central Government is about to introduce a new bill that will restructure and strengthen the drug regulatory process in India.

The Indian Central Government is about to introduce a new bill that will restructure and strengthen the drug regulatory process in India. The new structure is designed to centralize drug approvals and tighten the still somewhat lax manufacturing practices that have led to a proliferation of poor ethical practices and substandard drugs. According to a cabinet note, a new independent Central Drug Authority of India (CDAI) will replace the Central Drugs Standard Control Organization, along the lines suggested by the former director of the Indian Council of Scientific and Industrial Research (CSIR), Dr. R.A Mashelkar's expert committee in 2003. The CDAI will be responsible for the development and definition of basic standards, will provide technical vision and ensure that for every activity there is a clear policy framework and efficient supervision to ensure a uniform legislation. Furthermore, the government's plans disclose the establishment of ten (10) new divisions to be headquartered in Delhi and will take up specific roles, including regulation, enforcement, legal and consumer affairs; biotechnology products; pharmacovigilance/drugs safety; medical devices/diagnostics; imports; quality control; and Indian systems of medicine.

The States will continue to grant drugs sales licenses, but responsibility for the manufacturing licenses is to move over a five-year period to the CDAI. Additionally, the penalty for conducting clinical trials without permission is to be raised to 10 years' imprisonment with a fine of Rs.20 lakh (~US\$50,000). The Drugs Controller General (DCG) is to become Additional Secretary, and two Additional Drugs Controllers will work under him, one on Indian systems of medicine and the other on the remaining issues. Two new zonal offices are to be set up in Hyderabad and Chandigarh, and 114 posts created on top of the 82 currently sanctioned, of which 29 lie vacant. The extra cost of expansion, estimated at Rs.3 crore, is to be met through new fees for inspection and registration, and licenses for manufacturers, new products and clinical trials.

These new proposals will streamline licensing and improve quality control monitoring. Furthermore the proposed changes should bring in more efficiency and allow time for more thorough review of applications. The new proposals for centralization of the regulatory process, which are more aligned with the rest of the world will strengthen the pharmaceutical industry in India and will further improve its standing with the rest of the world

C. History of U.S.- India Cooperation in Science and Technology

1. Background

Science and Technology (S&T) cooperation between India and the U.S. has had a long history of more than fifty years and is characterized by successful and productive exchange of scientists and scientific ideas, joint workshops and conferences, joint/collaborative research projects, training/fellowship programs and technology transfer in virtually all areas of Science & Technology - traditional and frontier¹. It is one of the oldest and most extensive bilateral S&T cooperation entered into by India. In the late 1950s, Indian and American scientists began to collaborate on agricultural research. This activity was expanded in the 1960s into other fields of science and education, and resulted through the facilitation of Consortia of American Universities in the establishment of the Indian Institute of Technology in Kanpur, the National Council of Educational Research & Training in New Delhi, and the initiation of some major projects in health sector on prevention and other aspects of parasitic & communicable diseases, nutrition, cancer, etc. Satellite Instructional Television Experiment (SITE) program was undertaken in the 1970s in collaboration between the U.S. National Aeronautic and Space Administration (NASA) and the Indian Space Research Organization (ISRO). Furthermore, the year 1974 was marked with the establishment of the Indo-U.S. Joint Commission on Economics & Commerce, Science & Technology, Education & Culture, and Agriculture. Pursuant to the establishment of this joint Commission, an S&T Sub-Commission was further established in 1975. The S&T Sub-Commission includes seven Working Groups in different areas: Material & Physical Sciences; Earth Sciences; Atmospheric & Marine Sciences; Energy; Environment & Ecology; Information S&T; Health, and Medical and Life Sciences. These Working Groups generally met concurrently with the meetings of the Sub-Commission. As a result of the activities of the S&T Sub-Commission numerous U.S.-India joint research programs and workshops were developed and implemented.

2. Specific S&T Programs, Initiatives and Agreements - Chronology

The Science & Technology Initiative - STI (1983)

1983 is noted for the establishment of the Science & Technology Initiative (STI), a new cooperative fast track program aimed at the enhancement of S&T collaboration in five specific areas, i.e. Agriculture, Health, Monsoon Research, Biomass Research and Engineering and Solid State Science. The National Science Foundation in the U.S. and the Department of Science and Technology in India were jointly charged with the implementation of the program, which operated on cost sharing basis for eight (8) years until 1991.

The U.S. India Fund - USIF (1987)

In January 1987, the two governments signed an agreement that established the U.S.-India Fund (USIF) with the goal of supporting joint activities such as workshops, exchange of scientists and experts, as well as joint research programs in the field of education, culture and sciences. The USIF was primarily financed through the use of U.S.-held rupees provided under U.S. Public Law 480 (PL 480) funds and facilitated through the U.S. Agency for International Development (USAID).² The USIF operated for eleven years and resulted in a large number of productive workshops and joint scientific projects.

The S&T Fellowship Program (1991)

S&T Fellowship Program was a parallel activity during the period 1991-94. Under this program seventy Indian scientists spent 3-12 months in the U.S. while ten U.S. scientists spending various time periods in India. The Program was supported primarily by the U.S. Agency for International Development (USAID).² The Department of Science and Technology (DST)¹⁵ of India played a major role in the success of this fellowship program.

Earth/Atmospheric Sciences MOU and Agriculture MOU (1997, 1998, 1999)

A Memorandum of Understanding (MOU) for scientific cooperation in the area of Earth and Atmospheric Sciences was signed between the Department of Space (DOS) and the Department of Science and Technology (DST)¹⁵ of the Government of India, and the National Aeronautics and Space Administration (NASA) and the National Oceanic and Atmospheric Administration (NOAA) of the United States of America on December 16, 1997, in Washington, DC. The MOU provides for exchange of data and derived products between the two countries.

Similarly, a MOU between the Indian Council of Agricultural Research (ICAR), New Delhi and Cornell University, Ithaca, New York for cooperation in the area of Agricultural Research was signed in November 1998. With

the signing of this MOU, both sides agreed to promote research, training and improvement of production techniques through exchange of faculty, scientists and technologists. This MOU called also for an exchange of genetic and breeding materials, as well as scientific literature, information and methodology. ICAR had signed a parallel MOU with Iowa State University during early 1998, as well a research cooperation agreement with the Texas Agricultural Experiment Station, Texas A&M University (July, 1997).

The DST-NSF Collaborative Research Program (1997)

A program for Indo-U.S. collaborative basic research projects was initiated in 1997. The cooperating agencies were: Department of Science & Technology (DST) in India and the National Science Foundation (NSF) in the USA. This program supports workshops and joint research projects in fundamental areas of science and technology. Proposals under this arrangement are submitted simultaneously to DST by the Indian collaborators and to NSF by the U.S. researchers.

The Indo-U.S. S&T Forum – IUSSTF (2000)

An agreement that established an Indo-U.S. Science & Technology Forum (IUSSTF)⁵⁸ was signed by India's Minister of Science & Technology, Dr. M. M. Joshi, and the U.S. Secretary of State, Ms. M K Albright, during the visit of President Clinton to India in March 2000. The Forum was formally launched by the Minister of Science & Technology, Dr. M. M. Joshi, on July 20, 2000. The objective of the Forum is to facilitate and promote interaction in India and U.S. between government, academia and industry, in science & technology. The Forum promotes research and development, transfer of technology, and creation of comprehensive electronic reference sources for Indo-U.S. S&T operation as well as electronic exchange and dissemination of information on Indo-U.S. S&T cooperation. It has been registered as a Society with the Office of the Registrar of Societies in New Delhi on June 23, 2000. The Forum is a grant making organizations that funds scientific and technological projects of mutual interest to India and the United States. It also facilitates collaborations between the U.S. and India through sponsored workshops, symposia and conferences (for example see the 2006 workshops in Bangalore and Manesar listed below with NIH Office of Technology Transfer (OTT) and Indian technology management professionals), Training programs, and Joint Centers⁴ for research and development. IUSSTF is headquartered in New Delhi and managed by the Executive Director under the leadership of a bilateral Governing Body consisting of seven Indian and seven American researchers and government representatives and with the support of India Science and Technology Partnership (INSTP)⁵⁹. Since its inception, IUSSTF has brought together more than 5,000 Indian and U.S. scientists and has helped identify scores of new areas for bilateral cooperation. Many of the projects sponsored by the Forum are related to biomedical research.

The objective of the Forum is to facilitate and promote interaction in India and U.S. between government, academia and industry, in science & technology.

American professional societies have begun to express an increasing interest in India and Indian scientists.

Indo-U.S. S&T Roundtables (2000)

In conjunction with Prime Minister Vajpayee's last visit to U.S., representatives from India and U.S. held the 2nd High Level Round Table on Science and Technology on September 15, 2000, at Washington, DC; the 1st roundtable was held in Hyderabad, during President Clinton's visit to India. Distinguished scientists and administrators from both countries participated in these meetings. Both meetings were co-chaired by India's Secretary of Science & Technology, and the U.S. Director of the Office of Science & Technology Policy and Assistant to the President. The round table aimed at discussing the new directions for the 21st century in Indo-U.S. collaboration in science and technology. A joint communiqué issued at the conclusion of the 2nd roundtable was presented to the visiting Prime Minister. The Round Tables and the Indo-U.S. S&T Forum (IUSTF) represent intensified efforts for closer cooperation and stronger partnership in science and technology.

American Professional Societies Interaction (2000)

American professional societies have begun to express an increasing interest in India and Indian scientists. For the first time in its 80-year history, the American Institute of Chemists elected an India-American – Dr. A.K.N. Nandedkar, Professor, Department of Biochemistry and Molecular Biology, Howard University, and Director, Genetics, Newborn Screening Service, Howard University Hospital, as its President for the year 2000 and 2001. One of the first actions of the newly elected president was to set up a chapter in India. Professional Societies representing Indian-American scientists maintain strong interaction with scientists in India. The presidents of the U.S. National Academies of Sciences and Engineering have also expressed a strong desire for further cooperation with India.

Indo-U.S. Science and Technology Agreement of 2005 - S&T (2005)

The Governments of India and the United States signed an umbrella Science & Technology (S&T) agreement in Washington on October 17, 2005. The purpose of the agreement is to strengthen the science and technology capabilities of the United States and India, to expand relations between the extensive scientific and technological communities of both countries, and to promote technological and scientific cooperation in areas of mutual benefit. The objective of this new agreement, which for the first time establishes an intellectual property rights protocol and other provisions necessary to conduct active collaborative research, is to accelerate cooperation between Indian and U.S. scientists in government agencies, private sector, and academia in such areas as basic sciences, space, energy, nanotechnology, health, and information technology that will advance scientific understanding and benefit both nations. The new science and technology agreement is also meant to complement the activity of the Indo-U.S. Science and Technology Forum (see above) by facilitating follow-on technical collaborations.

Next Steps in Strategic Partnership - NSSP (2004-2006)

The Next Steps in Strategic Partnership (NSSP) initiative launched in January 2004 allowed opening a dialogue and building trust on a number of sensitive areas, including high-technology trade, civil nuclear cooperation, space, and missile defense. The U.S.-India strategic partnership is rooted in shared values and is broad in nature and scope, with the two countries working together on global issues, including expanding economic freedom and democracy; ensuring plentiful sources of clean, safe, and reliable energy; protecting security; supporting innovation and technological advances; and promoting public health.

In March 2005 the U.S. and India agreed to build on this successful partnership, moving beyond the Next Steps in Strategic Partnership (NSSP) to a Strategic Dialogue. Energy Dialogue seeks to expand cooperation in areas such as clean energy and civil nuclear energy. Economic Dialogue includes, for the first time, a forum of chief executive officers (CEOs) from leading corporations to advise both governments on how to accelerate economic cooperation. The United States and India resolved to build a global partnership based on areas of cooperation announced at the summit between the U.S. President and Indian Prime Minister in Washington July 18, 2005 White House fact sheet:

The United States and India Successfully Complete Next Steps in Strategic Partnership (NSSP) in July 18, 2005.

The areas of cooperation are:

- Economic Matters
- Energy and Environment
- Space
- Democracy and Development
- Disaster Relief
- HIV/ AIDS

High Technology Cooperation Group (HTCG)

High Technology Cooperation Group (HTCG) formed between India and U.S., which is chaired by Under Secretary, Department of Commerce, U.S. and Foreign Secretary, Ministry of External Affairs, Government of India. HTCG focuses towards building knowledge economy through public-private participation in the areas of biotechnology, nanotechnology, defense and information technology.

S&T Fellowship Program

About fifty scientists from various universities and scientific institutions in India come to U.S. annually for advanced research and training under the following three (3) fellowship programs (a) Biotechnology Overseas Associates Program of Department of Biotechnology; (b) Raman Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR) and (c) Better Oppor-

tunities for Young Scientists in Chosen Areas of Science and Technology (BOYCAST) fellowship of Department of Science & Technology. These short and long-term fellowship programs not only provide state-of-the-art research facilities to Indian scientists but also enable them to build long-term relationship with host institutions to pursue future cooperative activities

D. U.S.-India Cooperation in Health and Biomedical Research

1. Bilateral Agreements between the U.S. and Indian Governments

Indo-U.S. cooperation in health and biomedical research has a long and productive history of more than three decades. This collaboration continues to grow, as evidenced by an increasing number of grants, bilateral agreements, programs, and technical assistance initiatives. Indo-U.S. continued collaboration in biomedical research has resulted in increasing scientific knowledge, improving public health, and controlling, preventing, and eliminating diseases.

In June 2000 the two countries established a framework for collaboration on the Prevention of Sexually Transmitted Diseases (STDs) and HIV/AIDS. Following that, in a joint statement on July 18, 2005, (see above under NSSP) Prime Minister Manmohan Singh and President George W. Bush committed the two countries to further strengthen cooperation in the fight against HIV/AIDS. They agreed to continue to expedite U.S. Food and Drug Administration (FDA) review of generic Indian anti-retroviral drugs (ARVs), collaborate in basic sciences, product development and clinical trials, establish a corporate fund for HIV/AIDS as detailed below, expand HIV/AIDS workplace programs and increase access to safe, effective, quality anti-retroviral drugs.

Subsequently, Prime Minister Manmohan Singh and President George Bush issued yet another joint statement in New Delhi on March 2, 2006. This later statement stemmed from an extensive review of the progress made in deepening the global partnership between the two countries since the earlier statement of July 2005. In the March 2, 2006 statement the two leaders expressed satisfaction with the progress in many areas. With regards to cooperation in the medical front the joint statement expressed satisfaction with the expedited U.S. FDA drug approval processes that strengthen the combat against HIV/AIDS at the global level and further encouraged greater corporate participation to meet this challenge, including participation through the Indo-U.S. Corporate Fund for HIV/AIDS. The March 2, 2006 statement also reiterated plans to expand bilateral efforts and continue cooperation in the area of medical research as well as strengthen technical capacity in food and drug regulation in India and address the concern on avian influenza. The statement further emphasized the commitment of both countries to reaching out to the private sector for development of new medical products.

The March 2, 2006 statement also reiterated plans to expand bilateral efforts and continue cooperation in the area of medical research...

India further agreed to host a meeting of the International Partnership on Avian and Pandemic Influenza in 2007. The U.S. Department of Health and Human Services (HHS) has been committed to post public health experts in India for collaborative work on avian influenza and other emerging infectious diseases. The joint statement emphasized the sustained commitment by the United States Agency for International Development (USAID)² to provide financial and technical support to WHO for working with India and strengthening its capabilities to combat neglected and emerging diseases (see tuberculosis below).

Institutions in the two countries are working together in biomedical research and HIV/AIDS vaccine development. A senior U.S. researcher has been detailed to join other U.S. public health scientists working on HIV/AIDS with the Indian Council of Medical Research (ICMR),¹¹ Department of Biotechnology (DBT),¹⁴ and National AIDS Control Organization (NACO).⁶⁰ Joint efforts are under way to enhance the capacity of Indian institutions to conduct clinical trials. A Center of Excellence in Clinical Research has been established in Chennai with support from the U.S. Department of Health and Human Services. An Indo-U.S. Corporate Fund for HIV/AIDS has been established, managed by the ICICI Bank and the GIVE Foundation in India. With contributions from Indian and U.S. businesses, the Fund is intended to increase resources to fight HIV/AIDS in India. Within the first month of the Fund's establishment, six companies have pledged a total of \$1.2 million. Many more companies have indicated strong interest in providing funding, corporate expertise, or products and services.

Through an expedited review process, the FDA has approved 15 single-entity and co-packaged versions of previously FDA-approved brand name anti-retroviral drug preparations. Thirteen of the 15 ARVs are manufactured by Indian pharmaceutical companies. The Government of India has requested assistance from the FDA in its efforts to raise the capability of the Indian drug-approving agency. A team from the U.S. FDA visited India to discuss technical cooperation in this important area.

The U.S. and India are cooperating in many other important health areas, such as tuberculosis, malaria, reproductive health, maternal and child health, urban health, environmental and occupational health, vaccine development and evaluation, and disease surveillance. This collaborative work is being done under the auspices of a number of agencies, through bilateral agreements and other initiatives.

In the area of tuberculosis for example, the U.S. Ambassador to India David C. Mulford and the World Health Organization (WHO) representative to India Salim Habayeb signed a joint agreement for tuberculosis control in India on September 26, 2006 in New Delhi. In this agreement the United States through the United States Agency for International Development (USAID)² has provided \$4.17 million in funds to WHO for research and state level imple-

Within the first month of the Fund's establishment, six companies have pledged a total of \$1.2 million.

Medical professionals from the U.S. and India have developed plans and strategies to establish schools of public health in India.

mentation of the national disease control program in India. The United States has invested \$40 million in the fight against tuberculosis in India since 1998⁴.

It is important to note that tuberculosis is one of the leading causes of morbidity and mortality among the adult population (18-59 years) in India. India has more cases of tuberculosis than any other country in the world and twice as many as China, the next highest. Each day, one thousand Indians die from tuberculosis, meaning that social and economic losses due to the disease are enormous, costing about \$3 billion per year.

USAID² and WHO have achieved significant progress through their programs and collaborations in the past ten years in India. In addition to tuberculosis, their partnerships have resulted in preventing and controlling diseases like malaria and avian influenza in India. USAID investments in India in the area of neglected and emerging diseases have exceeded \$56 million. These investments helped build and strengthen the capabilities of local institutions and have leveraged resources from other development partners.

Medical professionals from the U.S. and India have developed plans and strategies to establish schools of public health in India. These schools will develop a cadre of public health experts and policy makers for programs to detect, prevent, and control diseases. HHS currently does and will continue in the future to provide technical and financial support for this initiative.

The U.S. Government is also India's committed partner in the fight against polio. The U.S. has been working with the Government of India to ensure success in the final push to eliminate polio from India. The U.S. has been providing technical and financial support to India's polio elimination efforts by assigning long- and short-term technical staff, providing vaccine, and supporting surveillance and social mobilization networks.

The U.S. Government will continue to support public-private partnerships, such as the collaboration that led to the development of a candidate vaccine against rotavirus (Bharat Corp.). The human rotavirus strain that forms the basis for this vaccine was provided to Bharat through the facilitation of the Center for Disease Control (CDC).⁵ Financial support for this project has been provided by the PATH'S Children Vaccine Program⁷ at Program for Appropriate Technologies in Health (PATH),⁶ an affiliate of the Bill and Melinda Gates Foundation (Seattle, WA). In this partnership, investigators from Indian and U.S. institutions have developed a promising candidate vaccine that is currently undergoing evaluation. If successful, this vaccine would prevent a substantial number of childhood deaths in India and other regions that are due to rotavirus (see more details on this project under the DBT section below). Furthermore, a new patented technology related to rotavirus vaccine has been recently licensed from the NIH³ to four Indian vaccine producers. More details about this project will be provided below in the section describing the collaborations between the NIH³ or NIH/OTT and India.

2. Specific Programs in Health and Biomedical Research

Within the framework of the U.S.-India S&T Cooperation, collaborative efforts in the health sciences have been particularly prominent. Special initiatives have been undertaken over the years in efforts to advance cooperation more rapidly and effectively in some areas. Some of the most prominent and successful programs are described below. The listed programs are funded by Indian and U.S. government money, where on the U.S. part, the NIH³ through its appropriate Institutes or Centers is the main agency responsible for the distribution and administration of the funds.

Indo-U.S. Vaccine Action Program (VAP)^{1,4,61 63, 65}

One of the most important and successful of the collaborative programs and initiatives has been the Indo-U.S Vaccine Action Program (VAP).

The VAP had its origin in 1984 when Dr. Fred Robbins, a U.S. Nobel Laureate in Medicine, visited India and prompted discussions of the possibility of taking advantage of advances in research technology to address needs for new and better vaccines for diseases of importance to India. These discussions, under the auspices of the Health Medical and Life Sciences Working Group of the Indo-U.S. S&T Sub-Commission, led to a series of actions that ultimately resulted in the signing of a Government-to-Government Memorandum of Understanding (MOU) for the VAP in July 1987. The cooperating agencies of the VAP are the Ministry of Health & Family Welfare, and the Indian Council of Medical Research on the Indian side and the Department of Health and Human Services (HHS) and the United States Agency for International Development (USAID)² on the U.S. side. The National Institute of Health (NIH)³ and more specifically the National Institute of Allergy and Infectious Disease (NIAID)⁴ within the NIH are key players in executing and funding the VAP program.⁶¹ A similar program was established for cooperation on contraceptive and reproductive health research.

The VAP supports a broad spectrum of activities relating to immunization. The program was designed originally to encompass laboratory-based research, epidemiological studies, field trials, vaccine quality control, and delivery of vaccines. Under the VAP, U.S. and Indian scientists carry out collaborative research projects directed toward development of vaccines and immunodiagnostic reagents, or addressing other issues which are important for vaccine research. All work is carried out within areas designated as VAP priorities by the VAP Joint Working Group (JWG) that is comprised of scientists and officials from both countries. The JWG, co-chaired by one U.S. and one Indian representative, establishes the policies and scientific directions for the program, makes decisions on major activities, and provides scientific oversight and evaluation.

On the Indian side, the JWG is called the “Apex Committee” and is appointed by the Prime Minister. As a committee appointed by the Prime Minister,

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Apex has the power to review and approve activities on the Indian side. This, coupled with the special authority given to the Indian Department of Biotechnology (DBT)¹⁴ by the VAP MOU has given this program an extraordinarily workable administrative system in India in which decisions can be made rapidly. Many projects, for example, have been reviewed and approved in a few months and scientist exchange visits in as little time as two weeks.

Funding of VAP

Funding for the Vaccine Action Program is provided by the Department of Biotechnology (DBT)¹⁴ of the Government of India and the Public Health Service (PHS) of the U.S. Department of Health and Human Services. Research awards are made to U.S. institutions through the National Institute of Allergy and Infectious Diseases' Division of Microbiology and Infectious Diseases (DMID)⁶³ at the NIH. Awards to the Indian institutions are made through the Indian Department of Biotechnology (DBT).¹⁴ Financial support for VAP has been provided also by the Starr Foundation,⁶² the Interim Fund,⁸ the Children's Vaccine Program (CVP)⁷ of PATH, and the Bill and Melinda Gates Foundation through the Malaria Vaccine Initiative (MVI).

NIAID Grants under the VAP

Extramural U.S. investigators may be funded through the NIH R03 mechanism. The R03 grant provides up to \$50,000 direct costs per year for up to two years. The R03 awards are not renewable. Information about R03 grants may be found under a new VAP Program Announcement (PA-07-093).⁷⁷

Intramural NIH investigators and other Federal scientists may be eligible for research support of comparable duration and scope through various inter-agency agreements.

In addition, information about a NIAID International Research in Infectious Diseases (IRID) R03 Program (PAS-04-111), which provides support to "institutions or organizations located in resource-constrained countries," is also available online.⁷⁶ This mechanism may also provide Indian institutions working on VAP projects with additional funds to expand their research focus and collaborations.

Priorities under the VAP

Priorities under VAP include: acute respiratory illnesses, rotavirus, cholera, dengue, leishmaniasis, rabies, HIV/AIDS, tuberculosis, malaria, and other emerging and re-emerging infectious diseases. Progress related to these priority diseases are given below under the section "The Role of the Indian Department of Biotechnology (DBT) in the U.S.-India Collaborations."

Useful informational web links for the VAP Program:

- Department of Biotechnology (India)⁷⁰
- All India Institute of Medical Sciences⁷¹
- National Institute of Immunology (India)⁷²

The R03 grant provides up to \$50,000 direct costs per year for up to two years.

- Indian Council of Medical Research⁷³
- HHS, Office of Global Health⁷⁴
- Fogarty International Center at NIH⁷⁵

It should be noted that the National Institutes of Health (NIH) Director Elias A. Zerhouni, M.D., and Secretary of the Department of Biotechnology in India, Maharaj K. Bhan, M.D., renewed the VAP agreement on May 3, 2007, in Bethesda, for another five-year period.⁶⁴

International Centers for Excellence in Research (ICER) at the National Institutes of Allergy and Infectious Diseases⁶⁷

The goal of the ICER program is to develop a sustained research program of excellence in areas of high infectious disease burden through partnerships with scientists in developing countries. As an initial part of this program NIAID through its DMID division, is supporting the establishment of several international centers of excellence in research. While focused on clinical research in infectious disease, each center will have the capability to address a range of research and training needs. Scientific areas include all infectious diseases except HIV (e.g., TB, malaria, STDs, diarrheal diseases, respiratory diseases, and vector-borne diseases).

In the initial stages, the goal of this program is to support core infrastructures containing high quality immunological, microbiological, biostatistical, epidemiological and clinical research capability. Development of in-country research capability in areas of high public health importance will be a major emphasis of the ICER Program.

The Indian ICER in Chennai, India will have a primary affiliation with the Tuberculosis Research Centre (TRC),⁶⁶ which is a permanent research institution of the Indian Council of Medical Research (ICMR),¹¹ an autonomous organization under the Ministry of Health and Family Welfare, Government of India. In addition, the TRC maintains a number of academic and research linkages with other Indian institutions, which may serve as collaborating ICER sites.

The TRC has been primarily focused on tuberculosis research and on training for tuberculosis research and control. In addition to well-equipped laboratories for the conduct of bacteriology, immunology, molecular biology, pathology and biochemistry research, the TRC has inpatient wards, outpatient clinics, field sites and epidemiologic teams. Recent or ongoing activities include clinical trials to evaluate principles of chemotherapy for both pulmonary and extra-pulmonary tuberculosis, development of immunologic and molecular-based diagnostics, mycobacterial genomics, epidemiologic studies on tuberculosis incidence and prevalence, as well as operational research on tuberculosis control. In addition to the support of the Indian Council of Medical Research, the TRC has established partnerships with a number of other international agencies.

While focused on clinical research in infectious disease, each center will have the capability to address a range of research and training needs.

Four additional projects have been recommended for funding by the eighth CRHR Joint Working Group meeting held in September 2006.

Chennai and its environment also provide opportunities for the study of many other infectious diseases. The NIAID Laboratory of Parasitic Diseases has had a lengthy history of collaboration with the TRC on pathogenesis of lymphatic filariasis, and is actively involved in ongoing studies on epidemiology, immunology and chemotherapy of filariasis in the region. The TRC has also recently established an HIV laboratory, and will be involved in studies on the interaction of HIV with TB and other infectious diseases.

The aim of the DMID program has been to expand opportunities for research collaborations on infectious diseases, and for research training, at the TRC and its affiliated institutions. Topics of interest include but are not limited to tuberculosis, acute respiratory infections, parasitic and other vector-borne diseases.

Indo-U.S. Contraceptive Research Program (CRHR)⁶⁸

The Indo-U.S. Contraceptive Research Program was established in 1997 to promote contraceptive development and reproductive health research; specific areas addressed within this program include basic clinical and applied research related to barrier and immunological methods for contraception and sexually-transmitted disease (including HIV infection) prevention, microbicide and spermicide research, epidemiological studies, and social, behavioral and intervention research related to reproductive health - studies of sperm maturation, motility and death, endometrial infertility, and vaginal antimicrobial contraceptives. Funding provided by the Department of Biotechnology¹⁷ of India, the National Institute of Child and Human Development (NICHD) at the NIH, the Interim Fund,¹¹ Office of AIDS Research (OAR)¹² at the NIH, and the CONRAD Program,¹³ a U.S. program dedicated to reproductive health and HIV prevention.

The DBT Annual report of 2006-2007 details the progress of this important program. It reports on 11 projects that have been completed, and 12 projects that are ongoing. Four additional projects have been recommended for funding by the eighth CRHR Joint Working Group meeting held in September 2006. For more details about the various projects the reader may obtain the 2006-2007 annual report by contacting DBT offices in New Delhi.

The Indo-U.S. Disease Surveillance Program

The Indo-U.S. Disease Surveillance Program was established in 1997 to assist Center/State efforts to strengthen India's disease surveillance system. The program objective is to assist the Indian Council for Medical Research (ICMR)¹¹ and WHO to establish a Field Epidemiology Training Program. Funding for this program comes from ICMR,¹¹ NICD,¹² CDC,⁵ and the Interim Fund.⁸

The Indo-U.S. Brain Research Program

The Indo-U.S. Brain Research Program was established in 1999 to promote neuroscience and mental health research through targeted workshops to stimulate joint proposals. Funding for this program is provided by the National

Institute of Mental Health (NIMH), the Department of Biotechnology¹⁴ of the Department of Science and Technology¹⁵ in India, and the National Brain Research Center of India.¹³

HIV/AIDS Prevention Research Program

The HIV/AIDS Prevention Research Program was established in 2000, to promote a range of HIV/AIDS and STD prevention research efforts, including behavioral prevention strategies and epidemiological and operational research on HIV/AIDS and STDs, including surveillance, STD treatment, and reproductive health and vaccine interventions. Funding comes from the NIH³ (U.S.) and ICMR¹¹ (India).

Maternal and Child Health Research Program⁶⁹

The Maternal and Child Health Research Program was established in 2000 to promote research in areas related to maternal and child health and development (MCHDR) of research, including but not limited to identification of and development of intervention to reduce risk factors for maternal morbidity/mortality, adverse birth outcomes (low birth weight, micronutrients), disease prevention (including reproductive tract infections, maternal-to-child transmission of HIV). Basic, clinical and applied research to address the reduction of birth defects, genetic disorders, and developmental disabilities, is encouraged. The MCHDR also covers research on systems/methods of traditional medicine, reproductive health including birth practices, evaluation of newer contraceptives and social-behavioral factors that impact on the health of mothers and children.

NIH Visiting Researcher Program

At the end of 2006 there were 276 Indian researchers on the NIH campus (includes 217 Visiting Fellows, 49 Visiting Scientists, and 6 Volunteers, 2 Guest Researchers, and 2 Exchange Scientists).

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3. The Role of NIH in the U.S.- India Collaborations

The National Institutes of Health (NIH), a public health agency of the Department of Health and Human Services of the U.S. government based in Bethesda Maryland, is supporting medical research programs around the globe. The NIH recognizes the importance of improving public health in developing countries and dedicates a large portion of its extramural grants of approximately \$28 billion annually to the support of medical research in developing countries, India included. The financial support for medical research in India covers a large range of diseases and comes from almost every one of the 27 Institutes and Centers that constitute the NIH. Research funds from the NIH may go directly to an Indian research institution or to a U.S. institution that collaborates with an Indian organization. Some of the most prominent projects and collaborations supported by the NIH in India

are provided below and listed according to the granting institute:

NCCAM (*National Institute for Complementary and Alternative Medicine*)

- The Christian Medical College (Vellore, India),¹⁷ the Ayurvedic Trust, and Bastyr University (U.S.) have developed collaborations to investigate the safety and efficacy of Ayurvedic medicine.¹⁶ It should be noted that Bastyr University at Seattle, Washington is one of the world's leading academic centers for advancing knowledge in the natural health sciences. A twenty-eight-year pioneer in natural medicine, Bastyr continues to be in the forefront of developing the model for 21st century medicine. (FY 05-06)

NCI (*National Cancer Institute*)

- SHARE India-MediCiti Hospital (India) and Johns Hopkins University (U.S.) are collaborating to study markers of progression to cervical cancer in rural India. This project is part of NCI's Specialized Programs of Research Excellence (SPORE)¹⁸ to promote interdisciplinary research and to speed the bi-directional exchange between basic and clinical science to move basic research finding from the laboratory to applied settings involving patients and populations. (FY 04-08)

NHLBI (*National Heart, Lung, and Blood Institute*)

- The All India Institute of Medical Sciences (AIIMS)¹⁹ in New Delhi has joined Duke University Medical Center in the Surgical Treatment for Ischemic Heart Failure (STICH) trial. Researchers are investigating the benefits of medical versus surgical intervention for patients with obstructive coronary disease and congestive heart failure. (FY 05-09)

NIA (*National Institute of Aging*)

- TN Medical College/Nair Hospital (India) and Mount Sinai School of Medicine in the U.S. have built research capacity for dementia and age-related cognitive decline research in Mumbai. (FY 04-06)

NIAAA (*National Institute on Alcohol Abuse and Alcoholism*)

- Investigators from the Drug Abuse Information and Research Center in Mumbai and the Sloan-Kettering Institute for Cancer Research in New York have collaborated on the STEP program, an alcohol and HIV prevention education program. The objective is to develop a program to prevent HIV risk behaviors and alcohol abuse among adolescents in India responsive to the cultural and socioeconomic issues that place adolescents there at risk for both alcohol abuse and HIV transmission. (FY 04-06)
- Researchers from the Sangath Society for Child Development and Family Guidance (India) and the Alcohol Research Group, Public Health Institute in Berkley, California have studied population drinking patterns and HIV risk, in Goa, India. (FY 04-06)

NIAID (*National Institute of Allergy and Infectious Diseases*)

- Collaborators from the Institute of Molecular Medicine (India) and the

Research Triangle Institute (U.S.)²⁰ are studying immunity to vaccines and infection in the Population Genetics Analysis Program (FY 05-09).

- Researchers from the All India Institute of Medical Sciences (AIIMS)¹⁹ and New York University are working towards the design of broadly neutralizing anti-HIV antibody responses, a primary goal in the race for an efficient HIV vaccine. (FY 05-09)
- Scientists from the Mumbai District AIDS Control Society and the University of California have collaborated in efforts to perform an intervention for male STD patients in India. (FY 00-06)

NICHD (*National Institute of Child Health and Human Development*)

- Researchers from the National Council of Applied Economic Research²¹ (India) and the University of Maryland are studying parental education and child outcomes. (FY 04-07)
- National Council of Applied Economic Research²¹ and College of Behavioral and Social Sciences (U.S.) researchers have studied the determinants of maternal and child health in India. (FY 03-06)

NIDA (*National Institute on Drug Abuse*)

- Tata Institute for Fundamental Research (India) and University of Arizona researchers have collaborated on a study of Fos, Jun, and synaptic plasticity. (FY 04-06)

NIDDK (*National Institute of Diabetes and Digestive and Kidney Diseases*)

- Researchers from St John's Medical College (India)²² and the Massachusetts Institute of Technology (U.S.) have been studying human amino acid requirements. (FY 99-07)
- Researchers at the LTM Medical College (Mumbai India) under a grant from NIDDK have investigated T2*/T2 calibration and application to magnetic resonance (MR) of heart iron. (FY 03-06)

NIMH (*National Institute on Mental Health*)

- Scientists from the National Brain Research Center¹³, an Institute of the Department of Biotechnology (DBT) in India, and the University of Texas Health Science Center are studying human brain CYP p450s and psychoactive drug metabolism. (FY 04-07)
- Researchers from the National Institute of Mental Health and Neurosciences (NIMHANS) in India and Johns Hopkins University have studied cellular tropism and reservoir in the brain with HIV-Clade C. (FY 04-06)
- Schizophrenia Research Foundation (SCARF) in Madras, India, and Indiana University scientists have studied visual processing in schizophrenia and schizotypal personality disorder. (FY 04-06)
- Researchers from the International Institute for Population Sciences (India) and the University of Connecticut Health Center have studied male sexual concerns and prevention of HIV/STDs in India. (FY 02-06)
- Dr. Ram Manohar Lohia Hospital (India) and the University of Pittsburgh

researchers have studied genetic susceptibility in schizophrenia. (FY 02-06)

- Scientists at the YRG Centre for AIDS Research and Education in India, and Johns Hopkins University have performed a collaborative HIV/STD prevention trial. (FY 99-06)

NINDS (*National Institute of Neurological Disorders and Stroke*)

- Researchers from the National Institute of Mental Health and Neuro Sciences (NIMHANS) in Bangalore, India, and the University of Miami School of Medicine have studied neurological progression in HIV-1 and HIV-2 co-infection. (FY 02-06)

4. NIH Fogarty International Center Programs Useful For Collaborations in India

The Fogarty International Center (FIC)²³, the international component of the NIH, addresses global health challenges through innovative and collaborative research and training programs and supports and advances the NIH mission through international partnerships. In its 35 years history the FIC has grown in a substantial way to having a budget of \$64 million (2006), all invested in research, training, and capacity-building enterprise extending to over 100 countries and involving some 5,000 scientists in the U.S. and abroad.

According to FIC the total support provided to India by the NIH reached more than \$16.5 million in 2006. The number of Indian fellows at the NIH at the end of 2006 approached 300 as mentioned above.

Following are some of the international programs sponsored by the NIH/FIC aimed at supporting collaborative research between U.S. and scientists in developing countries. Support for U.S. - India joint research through these programs is emphasized and detailed below:

Fogarty International Research Collaboration Awards (FIRCA)²⁹

The Fogarty International Research Collaboration Awards (FIRCA) program was initiated in 1992 by the Fogarty International Center to foster international research partnerships between NIH-supported U.S. scientists and their collaborators in countries of the developing world. The program funds 3-year research partnerships between practicing scientists and physicians in the United States and abroad. Geographically, the emphasis is on partnerships between U.S. scientists and their colleagues located in developing countries. The program aims to benefit the research interests of both the U.S. principle investigator and the international research collaborator while increasing research capacity at the international site. The program has evolved since its inception with progressively more focus on the capacity development aspects of the award. In 1994, an AIDS-specific award, not restricted to developing or transition countries, was added (AIDS FIRCA).

- Tata Institute of Fundamental Research (India) and Yale University

researchers have utilized a Fogarty International Research Collaboration Award (FIRCA) to study early environment and the neurobiology of depression. (FY 04-06)

- A grant under AIDS FIRCA was granted to the Tuberculosis Research Centre (India) and Temple University to study apoptosis in tuberculosis in India. (FY 05-07)
- FIRCA award was granted to the University of California, San Diego and Tata Institute of Fundamental Research in India for the study of Genetic Analysis of Dendritic Targeting. (FY 02-06)
- FIRCA award was granted to Harvard University, School of Public Health and SRI Ramachandra Medical College & Research Institute of India for the study of lead exposure and outcomes amongst children in Chennai, India. (FY 03-07)
- FIRCA award was granted to the University of Virginia, Charlottesville and Bose Institute, India, for the investigation of replication control in *E. histolytica*. (FY 05-07)
- FIRCA award was granted to Stanford University School of Medicine and Bose Institute, India for the study on identifying regulation of cell cycle gene networks in *E. histolytica*. (FY 06-08)

The Global Health Research Initiative Program (GRIP)³⁰

The GRIP program is intended to promote productive re-entry of NIH-trained foreign investigators into their home countries as part of a broader program to enhance the scientific research infrastructure in developing countries, to stimulate research on a wide variety of high priority health-related issues in these countries, and to advance NIH efforts to address health issues of global import.

- Researchers from the Centre for DNA Fingerprinting and Diagnostics in India, under a Global Health Research Initiative Program for New Foreign Investigators (GRIP) award, have studied the functioning of K-ras in lung type II epithelial cells. (FY 02-06)
- An additional GRIP was awarded to researchers at the Centre for DNA Fingerprinting and Diagnostics in India to study transcription termination and anti-termination in *E. coli*. (FY 02-06)
- GRIP award was granted to researchers at the Indian Statistical Institute to study statistical methods for mapping multivariate phenotypes. (FY 03-07)
- Under a GRIP award, researchers from the Hyderabad Eye Research Foundation are performing molecular genetic studies of retinitis pigmentosa in India. (FY 03-07)
- The AIDS International Training and Research Program (AITRP)²⁸

The AIDS International Training and Research Program (AITRP) began in 1988 as one of the first of a new generation of research training programs sponsored by the Fogarty International Center at the National Institutes of

Beginning in 2007, foreign institutions in low-and middle-income countries became eligible to apply for two-year planning grants.

Health. These programs provide training for scientists from institutions in low- and middle-income countries to strengthen HIV-related research and public health capacities at their institutions.

Grants for full research training programs are awarded to U.S. institutions with strong HIV- related research training experience and with HIV-related research collaborations with institutions in low- and middle- income countries. The grantees, in partnership with their foreign collaborating institutions, identify foreign health scientists, clinicians, and allied health workers from the foreign countries to participate in their joint research training programs. Beginning in 2007, foreign institutions in low-and middle-income countries became eligible to apply for two-year planning grants. The primary goal of this program is to build multi-disciplinary biomedical, behavioral and social science research capacity for the prevention, care and treatment of HIV/ AIDS and HIV-related conditions for those adults and children affected by HIV/AIDS in the collaborating country. AITRP makes provisions for training in the United States, in other countries, and in the home countries.

Support of Indians researchers under the AIDS International Training and Research Program (AITRP) at Johns Hopkins University, University of California, Los Angeles, Yeshiva University, Albert Einstein College of Medicine, Brown University, Tufts University, University of Pittsburgh, University of Alabama, Birmingham, New York University, University of Washington, and the University of California, Berkeley was provided for training to increase the proficiency and health professionals to undertake biomedical and behavioral research related to HIV/AIDS and to develop their skills in the conduct of clinical trials and prevention-related research.

International Clinical, Operational and Health Services Research and Training Awards (ICOHRTA)²⁴

The International Clinical, Operational and Health Services Research and Training Awards (ICOHRTA) is an innovative program to support integrated multidisciplinary, clinical, operational, and health services research and training collaborations between U.S. institutions and those in developing countries. The ICOHRTA provides opportunities for health professionals to train at the Ph.D., masters, and post-doctoral levels while working on international research projects related to a variety of non-communicable conditions.

International Clinical, Operational and Health Services Research and Training Awards (ICOHRTA) were granted to Washington University and the University of Alabama at Birmingham to support Indians researchers at the National Institute of Mental Health and Neurosciences in Bangalore for international research training in clinical sciences and to researchers the Madras Diabetes Research Foundation in Chennai for clinical research training for studies of CVD in India. The awards are intended to strengthen global capacity to characterize the disease burden of chronic conditions, to encourage

international efforts to apply current knowledge and new discoveries to clinical public health practice, and to evaluate practical and affordable therapeutic and preventive interventions and health service delivery for global health problems in the context of local needs and conditions.

The International Training and Research Program in Environmental and Occupational Health (ITREOH)²⁵

The Fogarty International Center, in collaboration with the National Institute of Environmental Health Sciences (NIEHS), NIH, and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), has developed the ITREOH program in order to train foreign health scientists, clinicians, epidemiologists, toxicologists, engineers, industrial hygienists, chemists, and allied health workers from developing countries and emerging democracies in both general environmental health and occupational health.

Program Design:

- Increase expertise in epidemiology, engineering, and other components of environmental and occupational health through short-and long-term training at U.S. institutions, which may lead to M.S. or Ph.D. degrees in epidemiology, engineering, toxicology, and other related areas;
- Increase laboratory expertise of technical assistants in foreign countries who are engaged in epidemiological and other studies related to environmental and occupational health through in- country, short-term, didactical, and technical training; and
- Expand ongoing collaborative training and research in environmental or occupational health between U.S. and foreign scientists.

Training Types:

- Training in epidemiology concepts and methods, environmental monitoring, industrial hygiene, field studies and other research related to environmental and occupational health that will lead to the M.S. or Ph.D. degree for individuals with previous field research experience;
- Training in epidemiology, field studies, environmental monitoring, industrial hygiene, and research related to environmental and occupational health that will lead to the M.S. degree for individuals without prior field research experience;
- Short-term comprehensive courses in epidemiology, toxicology, chemistry, industrial hygiene and environmental and safety engineering, with an emphasis on control of occupational injuries and illnesses, for health and safety professionals to be given in the U.S.;
- Training in laboratory procedures and research techniques related to environmental and occupational health for individuals with the M.S. or Ph.D. degree to be given in the U.S.; and
- Postdoctoral research training for foreign scientists who want to expand their abilities in the epidemiology, diagnosis, prevention and treatment of

environmental and occupational disease and injury. Postdoctoral training can take place both in the U.S. and in foreign countries.

In the last several years support of Indians health professionals under the International Training and Research Program in Environmental and Occupational Health (ITREOH) at the University of California, Berkley was provided for training in areas such as cancer epidemiology, toxicology, occupational medicine, and environmental epidemiology.

Minority International Research Training Grant (MIRT)²⁶

The MIRT program, now named the Minority Health and Health Disparities International Research Training (MHIRT) Grant Program, is now under new management at the National Center on Minority Health and Health Disparities of the NIH.²⁷ Grants under the MIRT support innovative programs that offer international professional students who are from health disparities populations and/or are underrepresented in basic science, biomedical, clinical, or behavioral health research career fields. The program is a component in the long-term NIH strategy to decrease health disparities between minority and majority groups in the U.S.

Under the Minority International Research Training Grant (MIRT) support for graduate and undergraduate U.S. minority students from the University of Alabama at Birmingham was awarded to study societal differences in the treatment of male and female children at the Society for Applied Studies in Kolkata, India. Another MIRT grant was awarded to students from Alcorn State University in Mississippi to study toxicology, parasitology, immunology, computer modeling, and ecology in collaboration with India health professionals.

Other NIH/FIC Programs to Support Collaborative Research between U.S. and India

Under the program of Brain Disorders in the Developing World: Research Across the Lifespan,³³ collaboration was established between Morehouse School of Medicine, Atlanta, GA and Malaria Research Centre/Regional Medical Research Centre (ICMR), India to study Cerebral Malaria Neurological Disorders in India. (FY 03-07)

International Research Scientist Development Award (IRSDA)³⁴ was given to the University of Pittsburgh at Pittsburgh, and Dayanand Medical College & Hospital in India for the study of Indo-U.S. Collaboration in Genomic Studies on Diabetes. (FY 05-07)

Under the International Collaborative Genetics Research Training Program,³⁵ support of Indian scientists at the Western Psychiatric Institute and Clinic at the University of Pittsburgh has been provided to study psychiatric genetics in India. This program aims to enhance and promote equitable international collaborations between investigators in the developed world and those in

developing countries where a base level of institutional infrastructure for the advancement of sustainable genetic science is already established.

Support of Indian health professionals under the International Training and Research Program in Population Health³⁶ at the Department of Cell Biology at the University of Virginia, and the University of North Carolina, Chapel Hill was provided to study issues of the reproductive processes, contraceptive development, contraceptive and reproductive evaluation, reproductive epidemiology, and social and behavioral factors that influence population dynamics.

Generally, the International Training and Research Program in Population Health supports research training of low- and middle-income country scientists with the long-term objective of strengthening these countries' research programs and institutions related to population health, including the study of demographic and reproductive processes. The program is intended to strengthen the ability of scientists from low- and middle-income countries to contribute to global population research efforts and to communicate and disseminate knowledge in support of population policies appropriate for their home countries and commensurate with established international guidelines.

Under the Centrally Coordinated Bioethics Program for India,³⁷ as part of the FIC International Bioethics Education and Career Development Award program, support was provided for researchers from the Indian Council of Medical Research to work on a two-year planning project of a centrally coordinated program in bioethics and research ethics in India. The project has the following objectives: to plan development of a uniform national bioethics curriculum for medical students, health professionals and researchers with the overall goal of strengthening the knowledge base in international bioethics and research ethics; to develop a centrally coordinated network of faculty to deliver this curriculum; and to develop a system to modify and improve this curriculum on an ongoing basis. This program is designed to support the development or expansion of graduate curricula in international bioethics related to conducting research in low- and middle-income countries.

Support was provided to two Fellows under the a Fogarty International Center/Ellison Medical Foundation Award to work in Vellore, India under the mentorship of Drs. Kenneth Mayer, Brown University, and Gagandeep Kang, Christian Medical College, on the molecular epidemiology of cryptosporidial infections in HIV infected individuals in South India. The FIC/Ellison Overseas Fellowships in Global Health and Clinical Research are a one year clinical research training experience for graduate level U.S. students in the health professions. This program presents an opportunity for highly motivated individuals to experience mentored research training at top-ranked NIH-funded research centers in developing countries.

- Each Fellowship is for a one-year period. The term begins with an intensive orientation program on the NIH campus in Bethesda, Maryland, followed

This program is designed to support the development or expansion of graduate curricula in international bioethics related to conducting research in low- and middle-income countries.

by approximately 10+ months of intense research training at the foreign site.

Under the International Tobacco and Health Research and Capacity Building Program,³¹ researchers from the Epidemiological Research Center in India and the University of Toronto are collaborating to strengthen monitoring of Indian tobacco mortality. (FY 04-08)

Under the same program, scientists from the Achutha Menon Centre for Health Science Studies in India and the University of Minnesota are performing cessation research and training in India and Indonesia. (FY 03-07)

Researchers from the Health Related Information Dissemination Amongst Youth (HRIDAY) and the University of Minnesota, under an International Tobacco program award, have collaborated on a study on mobilizing youth for action against tobacco in India. (FY 02-06)

A goal of another relevant program, the Stigma and Global Health Research Program,³² is to support research that leads to better understanding of the role of stigma in health throughout the world. Research in this area is the best hope for developing evidence-based interventions to prevent or mitigate stigma's negative effects on the health of individuals, families, and societies worldwide. Stigma prevents people from seeking diagnosis and care and from participating in research that could lead to effective interventions.

- Under the Stigma and Global Health Research Program, investigators from the Tata Institute of Social Sciences in India, and the University of California San Francisco are examining AIDS stigma and gender discrimination in patients treated in health care systems of Mumbai and Bangalore. (FY 05-09)

5. The Role of the CDC in the U.S.- India Collaborations

The Centers for Disease Control and Prevention (CDC)⁵ is one of the 13 major operating components of the Department of Health and Human Services (HHS) of the United States Government. Since it was founded in 1946 to help control malaria, CDC has remained at the forefront of public health efforts to prevent and control infections and chronic diseases injuries, workplace hazards, disabilities, and environmental health threats throughout the world. The CDC has particular focus on field-based epidemiology and laboratory training for in-country public health professionals that is especially relevant for health-related collaborations in India.

The CDC is composed of different Centers, Institutes and Offices (CIO) and a dedicated Office of Global Affairs (OGA). Almost all of the CIO organizations at CDC are active in sponsoring and supporting different health related programs in India and there are some CDC personnel stationed in India to

assist and provide expertise in various epidemiological studies. Some of the most active CIOs in India are: the National Center for Infectious (NCID),³⁸ National Center for HIV/AIDS, Viral Hepatitis, STD and TB prevention (NCHHSTP),³⁹ National Immunization Program (NIP),⁴⁰ National Center for Environmental Health (NCEH),⁴¹ Agency for Toxic Substances and Disease Registry (ATSDR),⁴² National Center for Chronic Diseases Prevention and Health Promotion (NCCDPHP),⁴³ and National Institute for Occupational Safety and Health (NIOSH),⁴⁴ the Environmental Protection Agency (EPA),⁴⁵ and the Public Health Practice Program Office (PHPPPO).⁴⁶

Following is a list of current activities and collaborations between the CDC and Indian government and research institutions. The list is arranged by alphabetical order, but each of the activities contains notes regarding the start date of the activity, the status and the sponsoring CIO:

Antimicrobial Resistance

The WHO External Quality Assessment Schemes (EQAS) proficiency and quality control program is conducted by NCID's Division of Healthcare Quality Promotion (DHQP). DHQP staff selects and package susceptible and resistant control strains of bacteria for testing and ships them to participating international laboratories in 40 countries, including India, who then test the strains and fax results directly to DHQP for analysis. DHQP staffs assess laboratory performance and send a cumulative summary to each laboratory as well as to WHO. Accuracy of testing has improved in areas where local or regional assistance is available. **CIO:** NCID *Start Date: Oct, 1996*

Status: ongoing

Birth Defects

As part of an international quality assurance program, NCEH staff provides dried blood spot quality control and performance evaluation materials for screening tests for a variety of diseases to international neonatal screening laboratories, including laboratories in India. The diseases, which vary by country, include congenital hypothyroidism, phenylketonuria, galactosemia, congenital adrenal hyperplasia, maple syrup urine disease, and homocystinuria. **CIO:** NCEH *Start Date: Jan, 1998* **Status: ongoing**

Blood Safety

In FY 2003, under a cooperative agreement with the American Red Cross (ARC), Global AIDS Program (GAP) India identified training priorities for a blood safety program. National leaders, including representatives from the National AIDS Control Program, met with representatives of the Indian Red Cross to review the assessment results of 81 blood banks and review plans for the quality control training program.

CIO: NCHSTP *Start Date: 2001* **Status: ongoing**

[E]ach year DVH sponsors an average of 20 international fellows for training in viral hepatitis laboratory research; these fellows spend an average of 2 to 4 years at CDC and then return to their home countries to continue their research.

Capacity Development

In FY 2003, Global AIDS Program (GAP) India supported data entry of more than 200,000 patient records into the GAP-supported information system (TB/HIV Information System, T/HIS) developed at the Government Hospital of Thoracic Medicine (GHTM). Hospital staffs were trained in the use of the information systems and monthly reports are now being generated. These data have helped both national and state-level officials recognize the critical need for developing quality care programs for HIV/AIDS and HIV/TB throughout southern India.

CIO: NCHSTP *Start Date: 2001* **Status:** *ongoing*

NCID's Division of Viral Hepatitis (DVH) has provided technical assistance to and conducted workshops and training sessions for public health scientists and laboratorians from other countries, including India. Overseas, DVH personnel have led courses focusing on the epidemiology and prevention of viral hepatitis, viral hepatitis surveillance, laboratory aspects and diagnosis of viral hepatitis, injection safety, blood safety, and medical practice safety. Laboratory training events often involve "wet" (active) laboratory components and last for several days. In addition, each year DVH sponsors an average of 20 international fellows for training in viral hepatitis laboratory research; these fellows spend an average of 2 to 4 years at CDC and then return to their home countries to continue their research.

CIO: NCID *Start Date: 1980* **Status:** *ongoing*

Cardiovascular Disease

In 1984, the current CDC-National Heart, Lung, and Blood Institute (NHLBI) Lipid Standardization Program (LSP) was implemented to offer combined total cholesterol (TC), triglyceride (TG), and high density lipoprotein cholesterol (HDL-C) standardization services. Standardization assistance is offered to any international laboratory involved in clinical trials and investigations supported by NHLBI, other institutes of the National Institutes of Health (NIH), and WHO – including laboratories in India. The goal of the LSP is to improve the laboratory measurement of cholesterol and related lipids so that they are measured with the accuracy and precision needed for detection, treatment, and prevention of cardiovascular disease.

CIO: NCEH *Start Date: Jan, 1984* **Status:** *ongoing*

Environmental Health

In 2002, India's Ministry of Health and Family Welfare and the U.S. Department of Health and Human Services signed a Joint Statement on Indo-U.S. Collaboration on Environmental and Occupational Health. The lead agency for India is the Indian Council for Medical Research (ICMR). The lead U.S. agency is CDC/ATSDR. The first meeting of the Joint Working Group was held in New Delhi in March 2003. The meeting brought together scientists and government representatives from India and the United States. Focus areas

identified as priorities for collaborative research and education projects include arsenic exposure and toxicity, indoor air pollution, emergency response, pneumonioses, chemical toxicants, children's environmental health, and gene-environment interaction. Under the auspices of the collaboration, ATSDR has funded a research project to evaluate the health effects of tremolite asbestos. U.S. members of the Joint Working Group include ATSDR, NCEH, NIOSH, EPA, the National Institute of Environmental Health Services, the Armed Forces Institute of Pathology, and the U.S. Geological Survey.

CIO: ATSDR *Start Date: Dec, 1999* **Status: ongoing**

A group of public health scientists in the United States and India is participating in an ongoing collaboration to foster improved environmental and occupational health in India. The group acts as a catalyst for the establishment of new environmental research collaborations among scientists in both countries. Topics on which NCEH scientists collaborate with Indian colleagues include air pollution, silicosis, and heavy metal poisoning. **CIO:** NCEH

Start Date: Apr, 2002 **Status: ongoing**

Epidemiology Service and Training

In late 1999, the Indian Government established a Field Epidemiology Training Program (FETP) based in the National Institute of Epidemiology (NIE) in Chennai (formerly Madras), Tamil Nadu State, India. This FETP is similar in design, methodology, and outcome to CDC's Epidemic Intelligence Service (EIS) and is one of many institutes of the Indian Council for Medical Research (ICMR), which focuses on infectious disease research. In 2003, CDC selected an experienced field epidemiologist to serve as a resident advisor (RA) and is working to place him in Chennai in 2004 through WHO/India. The RA will assist in training and mentoring FETP trainees as they apply their skills to solve real public health problems in India. Many strong partnerships and collaborations helped launch this program and will help sustain its growth over time. Currently, the program hosts trainees from six Indian states whose collective population is 200 million (of the country's total population of 1 billion). As soon as the Tamil Nadu program is established to the satisfaction of all partners, CDC will encourage its Indian partners to send stronger graduates to other states to begin satellite programs nationwide, helping the Indian government realize its goal of improving the population's health while building its own public health infrastructures.

CIO: EPO *Start Date: Jan, 2001* **Status: ongoing**

Gastroenteritis

NCID's Division of Viral and Rickettsial Diseases hosted a pathologist from the All India Institute of Medical Sciences (AIIMS) in New Delhi. Technical assistance was provided in the examination of gastrointestinal specimens, which included histopathologic evaluation and immunohistochemical assays

for adenovirus and rotavirus. **CIO:** NCID *Start Date: Oct, 2002*
End Date: Nov, 2002 **Status: completed**

Hepatitis

In collaboration with colleagues from the Sanjay Gandhi Institute of Medical Sciences in Lucknow, India, researchers from NCID's Division of Viral Hepatitis (DVH) are studying the transmission of hepatitis E virus (HEV), with particular emphasis on subclinical infections as a possible reservoir of the virus in a cynomolgus macaque model of the disease. The data obtained from these studies will add to current knowledge about the biology of HEV infection and help to develop strategies aimed at the prevention and control of these infections. In addition, DVH hosted a guest researcher from the Sanjay Gandhi Institute for a year to work on this project at CDC.

CIO: NCID *Start Date: May, 1999* **Status: ongoing**

HIV

In FY 2003, Global AIDS Program (GAP) India signed a cooperative agreement with the Indian Network of Positive People (INP+) to establish a pre-discharge family counseling center at the Government Hospital of Thoracic Medicine (GHTM), which has strengthened the linkages between clinical care, the affected communities, and HIV prevention at GHTM. The Government of Tamil Nadu has provided space for the counseling center on GHTM property and renovation plans have been developed. INP+ members regularly participate in meetings at GHTM and are becoming valued members of the HIV/AIDS care and prevention team at the hospital. GAP-sponsored activities at the GHTM, the largest AIDS care center in India, have been in place since 2001. In 2003, the GHTM averaged 300 HIV-positive outpatients per day, including 30 to 60 new patients. Between January and September 2003, the hospital admitted 6,857 patients and saw 9,832 new outpatients; quarterly reports demonstrate that the number of patients being seen is substantially higher compared to the previous year. Characterizing these patients epidemiologically and clinically will provide valuable information to both the state and national HIV/AIDS program as well as the National Tuberculosis Program. Under a cooperative agreement with the Tamil Nadu State AIDS Society (TNSACS), programs at GHTM are being strengthened, local ownership of the project is growing, and other key public and private medical institutions in the state are being included in the project.

CIO: NCHSTP *Start Date: 2001* **Status: ongoing**

As part of an international laboratory quality assurance program, staff from NCEH's Division of Laboratory Sciences (DLS) conducts evaluations for HIV antibody testing on dried blood spots from samples provided by laboratories in fourteen countries, including India. DLS also supports CDC's Global AIDS Program on quality assurance issues concerning confirmation of antibody testing in country and use of the new HIV rapid tests in resource poor countries. **CIO:** NCEH *Start Date: Jan, 1988* **Status: ongoing**

HIV/STD Prevention

In FY 2003, Global AIDS Program (GAP) India supported the National Advisory Committee for Quality voluntary HIV counseling and testing (VCT), which made significant progress in conducting regional workshops on VCT, reviewing and revising India's national VCT guidelines, and creating opportunities for communicating the importance of VCT at national and local forums. Representatives from the steering committee communicate via a designated Web site and meet regularly to review progress and make recommendations on the implementation of the national VCT program. GAP India also initiated youth activities in four high prevalence districts in the states of Tamil Nadu and Andhra Pradesh after consultation with state AIDS Directors.

CIO: NCHSTP *Start Date: 2001* **Status: ongoing**

In FY 2003, Global AIDS Program (GAP) India staff established excellent working relationships with the Government of India and bilateral, multilateral, and nongovernmental organization (NGO) counterparts at both the national and local levels, becoming valued technical advisors on HIV/AIDS within the U.S. Mission, donor community, and the Indian government. GAP India staff actively participated in the United Nations Theme Group and provided technical support to the Indian government for the second and third rounds of the Global Fund Proposals for HIV/AIDS, Tuberculosis, and Malaria. The Global Fund applications were successful in mobilizing almost \$150 million for HIV/AIDS, TB, and TB/HIV programs in India. GAP India worked with a network of Indian epidemiologists, biostatisticians, and behavioral scientists (IndiaCLEN) for technical support of GAP India's projects. IndiaCLEN members work closely with GAP Atlanta technical staff in order to ensure consistency of technical support and to further strengthen local capacity for HIV/AIDS. IndiaCLEN staff has become valued partners at the Government Hospital of Thoracic Medicine (GHTM), providing support in the use of the information system for data analysis.

CIO: NCHSTP *Start Date: 2001* **Status: ongoing**

In FY 2003, Global AIDS Program (GAP) India provided primary health care, HIV counseling, and referral services to people in slum communities in Pune, Maharashtra through a cooperative agreement with Project Concern International (PCI). The project was recently expanded from six to nine urban slum communities, serving a population of 154,000 and more than 400 HIV-positive individuals in their homes. More recently, after a review of data generated from the information systems at the Government Hospital of Thoracic Medicine (GHTM) and in consultation with GAP India and key officials from Tamil Nadu State, PCI initiated a second project in Salem, a high prevalence district in a rural area of Tamil Nadu, covering a population of approximately 170,000. Offices have been established in Salem and a memorandum of understanding with the district network of HIV-positive people was signed. Working with local leaders, networks of HIV-positive people, youth,

The project was recently expanded from six to nine urban slum communities, serving a population of 154,000 and more than 400 HIV-positive individuals in their homes.

Since January 2001, NIP has participated on GAVI's Board, Implementation Task Force, and Research and Development Task Force.

women's groups, and health providers, the project is becoming recognized as a model program for community care. Home health aides have been trained in HIV/AIDS care and counselors are beginning to carry out pre- and post-test counseling at the community level. In both Maharashtra and Tamil Nadu States, strong linkages have been established with local health care facilities, the national Tuberculosis Directly Observed Therapy-Short Course (DOTS) program, and social support programs. Representatives from the PCI project regularly participate in training programs and workshops at GHTM in order to facilitate linkages between hospital-based and community care programs.

CIO: NCHSTP *Start Date: 2001* **Status: ongoing**

Immunization

NIP's Global Immunization Division supports strengthening global childhood immunization programs through direct support to countries, through partners (such as WHO and UNICEF), and through participation in the Global Alliance for Vaccines and Immunization (GAVI). GAVI was initiated in 2000 with the primary goals of introducing new vaccines (e.g., hepatitis B, Haemophilus influenzae type b, and yellow fever), improving immunization coverage, and improving injection safety (for immunization) in the poorest countries – those with per capita GNP of under \$1,000. Funds exceeding \$1.2 billion have been made available to countries beginning in 2000 for these purposes, continuing for 5 years. CDC is one of many partners contributing to this effort, which is led by UNICEF, WHO, the Bill and Melinda Gates Foundation, the World Bank, and others. Since January 2001, NIP has participated on GAVI's Board, Implementation Task Force, and Research and Development Task Force. In India, funding supports routine immunization activities in Bihar and West Bengal through UNICEF.

CIO: NIP *Start Date: JAN, 2000* **Status: ongoing**

Influenza

In September 2003, the WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza in the Influenza Branch of NCID's Division of Viral and Rickettsial Diseases (DVRD) shipped out 241 kits for global influenza laboratory surveillance to U.S. state health departments, foreign national influenza centers, including centers in India, and other collaborating institutions. CDC provides a kit containing reagents for identification of influenza specimens for global influenza surveillance. This information is essential for the identification of variants and the timely inclusion of new variants into the influenza vaccine. DVRD also distributed kits for the identification of A(H5) and A(H7) viruses, due to the emergence of these novel subtypes in humans.

CIO: NCID *Start Date: Jan, 1991* **Status: ongoing**

Laboratory Diagnostics

The Model Performance Evaluation Program for HIV-1 antibody testing is an ongoing external assessment program provided by PHPPPO's Division of Laboratory Systems (DLS) that is available to laboratories worldwide. Twice a year,

six referenced survey specimens are shipped to laboratories in India for HIV-1 antibody testing. After each site tests the specimen panel, its results are sent to DLS. DLS staff analyzes the results and provide a summary report of the aggregate performance by method type and reagent manufacturer. The results for individual laboratories or laboratories by country are not evaluated, but each participating laboratory can compare its performance against the whole to identify potential problems and make improvements or changes in its testing process, as needed. **CIO:** PHPPO *Start Date: Jun, 1986* **Status: ongoing**

Laboratory Methods Development

PHPPO's Division of Laboratory Systems (DLS) provided assistance to India for laboratory renovations in Chennai, including finalizing equipment procurements and the selection of laboratory staff. DLS staff conducted a general quality control activities workshop in September 2003.

CIO: PHPPO *Start Date: Sep, 2003* **Status: ongoing**

Laboratory Standardization

Ensuring the Quality of Iodine Procedures (EQUIP) is a CDC standardization program designed to provide urinary iodine laboratories with an independent assessment of their analytical performance. The program, which is operated jointly by NCEH and NCCDPHP, will help laboratories monitor the degree of variability and bias in their urinary iodine assays. Information received from the program can then be used to eliminate bias and/or precision problems in the assay system; confirm the quality of analysis; and increase each laboratory's confidence level. Currently, 42 laboratories in 31 countries, including India, participate in the EQUIP program.

CIO: NCEH *Start Date: Jul, 2001* **Status: ongoing**

Malaria

NCID's Division of Parasitic Diseases is collaborating with the Malaria Research Centre on a cohort study on the epidemiologic, immunologic, and entomologic characteristics of malaria during pregnancy in India.

CIO: NCID *Start Date: Jun, 2002* **Status: ongoing**

Natural Disasters

At the request of and in consultation with WHO's Regional Office for Southeast Asia (SEARO), NCEH's Division of Environmental Hazards and Health Effects (EHHE) developed and presented a 1-week training course in June 2003 on the epidemiologic response in disaster settings to district health officers and WHO field staff from Gujarat, India. Gujarat was the site of a major earthquake that affected an estimated 37.8 million people and killed more than 17,000 in January 2001. **CIO:** NCEH *Start Date: Jun, 2003*

End Date: Jun, 2003 **Status: completed**

Noncommunicable Disease Prevention and Control

Through an assignee to WHO, NCCDPHP's Division of Adult and Community Health guides the work of the Mega Country Health Promotion Network.

In Alaska, out of 648 work-related deaths taking place in 1990-1999, one-third (217 cases, or 33% of the total) occurred among fishermen.

The Network was established to mobilize the world's most populous countries, including India, to address the transition of the global burden of disease from communicable to noncommunicable conditions and to promote health in a collaborative effort. Priority areas to be addressed through the Network have been identified by Mega country representatives. These include: school health as a key setting for primary disease prevention; key risk factors of chronic diseases (including tobacco, diet and nutrition, and physical activity) as an integrated approach to the field of chronic diseases; and behavioral risk factor surveillance as a tool for strengthening the evidence base for chronic diseases. Data collection on key behavioral risk factors began in 2003 by the Indian Council of Medical Research (ICMR) in New Delhi among a sample of 5,000 persons aged 15 to 64 in the urban areas of East Delhi, covering both slum and non-slum areas. This work links the data collection efforts in five other centers currently collecting behavioral risk factor data. In 2003, work also began on a data action report among the Mega countries to document how data collected on three key risk factors, tobacco use, diet/nutrition, and physical activity, are being used in the most populous countries to implement health policies and programs.

CIO: NCCDPHP *Start Date:* Mar, 1998 **Status:** ongoing

Occupational Safety and Health

Throughout the world, commercial fishermen labor in deadly environments. They endure isolated fishing grounds, high winds, seasonal darkness, extremely cold water and icing, and short fishing seasons, where very long workdays are the norm. These hazardous work conditions have a strong impact on fishermen's safety. In Alaska, out of 648 work-related deaths taking place in 1990-1999, one-third (217 cases, or 33% of the total) occurred among fishermen. This is equivalent to an annual fatality rate of 124/100,000 workers/year – 28 times that of the overall U.S. work-related fatality rate. NIOSH has a strong interest in improving safety and health outcomes for commercial fishermen and has an ongoing commitment to disseminate current knowledge on best safety practices and policies for these workers. In 2003, the Second International Fishing Industry Safety and Health Conference, IFISH II, was convened in September 2003 in Sitka, Alaska. The conference served as a primary means by which NIOSH fostered collaboration among fishing countries to address the global hazards of commercial fishing. The Alaska Marine Safety Education Association assisted with convening the conference. The U.S. Coast Guard supported the conference by assisting with program planning and providing fishing safety equipment and demonstrations during the event. Local support for program planning and speaker recruitment came from the Alaska Vocational Technical School in Seward, Alaska. The Food and Agriculture Organization provided scholarships for seven individuals from developing nations to attend the conference, including India, Pakistan, Sri Lanka, Chile, Tonga, and Senegal. Maritime Safety Agencies or other regulatory bodies sent

representatives from New Zealand, Australia, Namibia, Sweden, the Faroe Islands, and Canada. Nongovernmental organization (NGO) representatives were sent by Indonesia, Norway, and Australia. Publication of the proceedings from IFISH II (scheduled for 2004) will result in at least 30 new papers that will add significantly to the body of knowledge on this topic.

CIO: NIOSH *Start Date: Oct, 2000* **Status: ongoing**

Parasitic Diseases

Scientists from NCID's Division of Parasitic Diseases have collaborated with researchers from the Cysticercosis Working Group at the Christian Medical College (CMC) in Vellore to complete a reference diagnostic study. The study showed that although minor variance occurs in the diagnostic antigens from Indian parasites as compared to those from Latin America, the predictive values of tests based on these antigens remain unchanged. This is an important issue because of the extent of global travel. Another collaborative study on the systematic, definitive classification of single lesion (SL) neurocysticercosis cases and endemic prevalence is ongoing with participation from India (CMC), the Peruvian Cysticercosis Working Group, and NCID. The results of this study will provide a standardized, global definition of SL cases in neurocysticercosis as well as definitive prevalence data for SL in India and Peru.

CIO: NCID *Start Date: 2001* **Status: ongoing**

Researchers from NCID's Division of Parasitic Diseases (DPD) are involved in molecular epidemiologic studies of cryptosporidiosis and microsporidiosis, using clinical specimens from hospitals, case control or cohort studies, and animals and the environment. Goals of the study include determining the infection/contamination sources and the distribution of anthroponotic and zoonotic parasites, as well as identifying risk factors and transmission dynamics.

CIO: NCID *Start Date: Jan, 2002* **Status: ongoing**

Refugee Health

By law, NCID's Division of Global Migration and Quarantine (DGMQ) is responsible for overseeing the medical screening and health assessment of immigrants and refugees bound for the United States. This oversight responsibility involves assessments of the physicians (known as panel physicians) who perform the examinations overseas as well as assessing the laboratories and x-ray facilities used by these physicians. DGMQ staff assessed the activities of panel physicians in India in order to correct any deficiencies in screening for certain communicable diseases, including TB and HIV.

CIO: NCID *Start Date: Nov, 2000* **Status: ongoing**

Rotavirus

NCID's Division of Viral and Rickettsial Diseases is collaborating with two U.S. institutions (NIH and Stanford University) and two Indian institutions (the All India Institute of Medical Sciences in New Delhi and the Indian Institute of Science in Bangalore) to develop, test, and produce a live, oral rotavirus

Work to develop pilot lots of the two candidate vaccines in India has begun in collaboration with Bharat Biotech International Limited.

vaccine in India to prevent severe rotavirus diarrhea in children. The two candidate neonatal rotavirus vaccines being proposed represent the products of two independent research teams that have worked in parallel for more than a decade under the auspices of the Indo-U.S. Vaccine Action Program (VAP) and are now combining their efforts. The project involves three goals: vaccine production, vaccine testing, and surveillance. An Indian commercial partner with experience in vaccine development, Bharat Biotech International Limited, has been enlisted to help first with the preparation of a test lot of vaccine for clinical trials and then to prepare the vaccine for widespread use. The goal of this work is the production of a quality rotavirus vaccine in India that would be fully tested according to the best international standards for safety, immunogenicity, and efficacy and would become available for inclusion in the universal program for childhood immunization. The project is being supported by the Children's Vaccine Program at the Program for Appropriate Technology in Health (PATH), the Indian Government's Department of Biotechnology (DBT), WHO, and the National Vaccine Program Office. During FY 2003, Phase I studies of the NIH-manufactured candidate rotavirus vaccines in adults were completed. The trials demonstrated that the candidate vaccines were safe among Indian adults. The team then proceeded with developing protocols for testing of the NIH-manufactured vaccine in children 2 to 12 years of age and in infants 6 to 12 weeks of age. Work to develop pilot lots of the two candidate vaccines in India has begun in collaboration with Bharat Biotech International Limited. Multi-center surveillance for rotavirus disease among hospitalized children is being established at five sites in India in preparation for vaccine testing in FY 04. The project is now in Phase IIa clinical trials. **CIO:** NCID *Start Date: Jan, 1998* **Status: ongoing**

School Health

Through WHO, NCCDPHP's Division of Adolescent and School Health (DASH) provides technical support and recommendations for improving coordinated school health and HIV prevention programs to national school groups in the world's 11 most populous countries (known as the Mega countries) and in nine Global AIDS Program (GAP) countries.

CIO: NCCDPHP *Start Date: Nov, 1998* **Status: ongoing**

Surveillance

In FY 2003, Global AIDS Program (GAP) India supported the National Association for State and Territorial AIDS Directors (NASTAD) in continuing its collaboration with the Andhra Pradesh State AIDS Society (APSACS) to develop an epidemiologic profile of one of state's high prevalence districts (population 3.8 million). Working closely with staff from APSACS and a local medical college in order to build local capacity, the team reviewed existing data and used Epi Info for data entry and analysis. A preliminary draft of the District Epidemiologic Profile was presented to the Project Director of APSACS in September and plans are underway to expand the project to other

districts of Andhra Pradesh State. Other State AIDS Directors are requesting similar support from GAP India.

CIO: NCHSTP *Start Date: 2001* **Status: ongoing**

In September 2003, scientists from NCID's Division of Viral and Rickettsial Diseases (DVRD) traveled to India to meet with representatives of the Indian Council for Medical Research (ICMR) and the National Institute of Communicable Disease to discuss ongoing and future collaboration on emerging and reemerging infectious diseases and disease surveillance. Discussions focused on expanding existing collaborative networks for public health endeavors, including interagency and international partnerships, which would be beneficial to investigating and controlling outbreaks and to achieving overall public health goals. DVRD and ICMR agreed on developing mechanisms for scientific exchange and training in applied epidemiology, field investigations of disease outbreaks, virological diagnostics, and containment and handling of emerging disease viruses. DVRD staff will continue efforts to place a resident advisor with India's Field Epidemiology Training Program.

CIO: NCID *Start Date: Sep, 2003* **Status: ongoing**

Syphilis

Scientists in the Syphilis Serology Reference Laboratory in NCHSTP's Division of STD Prevention provided syphilis serology proficiency testing samples for 76 laboratories in 57 countries, including India. CDC administers the program, with WHO enrolling participants. CDC is responsible for preparing samples, sending them to the enrolled laboratories, grading results, and providing summary reports for three shipments per year. This program has been in place since 1988 and is a function of the WHO Collaborating Center for Reference and Research in Syphilis Serology.

CIO: NCHSTP *Start Date: Jan, 1991* **Status: ongoing**

Tobacco Control

In 1998, NCCDPHP's Office on Smoking and Health (OSH) and WHO's Tobacco Free Initiative (TFI) launched a Global Youth Tobacco Survey (GYTS) as part of a WHO/UNICEF-supported project on youth and tobacco. The GYTS is a school-based, tobacco-specific survey that focuses on adolescents aged 13 to 15 years, providing an in-depth assessment of students' knowledge, attitudes, and behaviors related to tobacco. The GYTS has been completed in 116 countries and is in process in 34 countries. Training is planned for 26 additional countries, including India. The GYTS also has been repeated in 12 countries, with another 22 countries planning to repeat the survey during 2004. For each country conducting the GYTS, OSH staff assist in the development and review of the final questionnaires; provide data collection answer sheets; process, edit and weigh all data; produce detailed tables; and provide a data diskette for individual analysis. OSH staff provides ongoing technical assistance regarding further analysis, interpretation of results, and report writing. Recent findings of the GYTS Collaborating

Scientists in the Syphilis Serology Reference Laboratory in NCHSTP's Division of STD Prevention provided syphilis serology proficiency testing samples for 76 laboratories in 57 countries, including India.

Group, entitled "Gender Differences in Global Youth Tobacco Use," were published in the August 2003 issue of the *Journal of School Health* (Vol. 73, No. 6). **CIO:** NCCDPHP *Start Date:* Dec, 1998 **Status:** ongoing

In early 2000, NCCDPHP's Office on Smoking and Health (OSH) and WHO's Tobacco Free Initiative (TFI) began the development and implementation of a Global School Personnel Survey (GSPS) as part of a WHO/UNICEF-supported project on youth and tobacco. The GSPS is a tobacco-specific survey of school personnel that provides in-depth assessment of behaviors, knowledge, attitudes, school curricula and policies regarding tobacco. For each country conducting the GSPS, including India, OSH Staff assist in the development and review of the final questionnaires; provide data collection answer sheets; process, edit and weigh all data; produce detailed tables; and provide a data diskette for further analysis. OSH staffs also provide ongoing technical assistance regarding further analysis, interpretation of results, and report writing. **CIO:** NCCDPHP *Start Date:* Jan, 2000 **Status:** ongoing

Staff from NCCDPHP's Office on Smoking and Health are working with WHO's Tobacco Free Initiative (TFI) to collect information on tobacco-related knowledge, attitudes, and behavior of nationally representative samples of medical doctors in WHO member nations. The Global Medical Doctor's Survey (GMDS) was piloted in 2003 in three sites in India and Myanmar. The GMDS focuses on doctors' personal smoking histories as well as the treatment approaches they use with patients. The next steps involve analyzing the pilot data and finalizing materials to be used during the survey's global implementation. **CIO:** NCCDPHP *Start Date:* Apr, 2000 **Status:** ongoing

The Indian Ministry of Health (MOH), in partnership with the Indian Council of Medical Research (ICMR) and NCCDPHP's Office on Smoking and Health (OSH), is preparing a joint report on Collaborative Approaches for Comprehensive Tobacco Control in India. The objective is to collate the evidence-based information on tobacco use in India, complemented with an analysis of the current situation and recommended proposals for future strategies to implement effective tobacco control. The report will be modeled after the U.S. Surgeon General Reports, published annually since 1964, which have become the evidence-based resource for tobacco use prevention and control in the United States. OSH is providing technical expertise for the development of the report. Two successful India and U.S. team working group meetings were held in October 2002 and June 2003. A joint India-U.S. release of the report is expected. **CIO:** NCCDPHP *Start Date:* Oct, 2001 **Status:** ongoing

Training

In FY 2003, Global AIDS Program (GAP) India trained hospital personnel at the Government Hospital of Thoracic Medicine (GHTM) in laboratory quality assurance. GAP India also helped establish a curriculum committee at GHTM. Under a cooperative agreement with the U.S. Health Resources and

Services Administration (HRSA) and the University of Washington, timelines for the development of training modules have been developed in consultation with the hospital staff and Tamil Nadu State AIDS Society (TNSACS). Training modules on the treatment of opportunistic infections and infection control were identified as the highest priorities. Roundtable discussions with key leaders in public health and HIV/AIDS in Tamil Nadu have been held to discuss training needs in the state, monitoring and evaluation, laboratory quality control, and other key topics.

CIO: NCHSTP *Start Date: 2001* **Status:** *ongoing*

Led by a Steering Committee consisting of WHO, CDC, the Danish Institute for Food and Veterinary Research, Institute Pasteur International Network, Health Canada, and the Netherlands' Animal Sciences Group, WHO Global Salm-Surv is an international network of over 800 individuals involved in foodborne diseases. The network's long-term mission is to reduce foodborne disease globally by enhancing laboratory-based surveillance and outbreak detection and response techniques. WHO Global Salm-Surv conducted eight training courses in FY 03 to help strengthen the skills of microbiologists and epidemiologists in laboratory-based surveillance and outbreak detection and response techniques. The courses promoted interaction with regional Field Epidemiology Training Programs. Each course had approximately 20 to 30 participants, with a total of approximately 200 people trained from 75 nations, including India. **CIO:** NCID *Start Date: 2000* **Status:** *ongoing*

Tuberculosis

In response to a technical assistance request from the WHO Regional Office for South-East Asia (SEARO), NCHSTP's Division of Tuberculosis Elimination (DTBE) has assigned a Medical Officer and recognized technical expert in TB prevention and control to SEARO. The assignee is providing technical assistance to assist in the implementation of improved TB control programs in India and the surrounding region; advise WHO, the World Bank, the Government of India, and other governments in the region on TB control strategies; and develop mechanisms to strengthen existing international partnerships and to forge new relationships that will optimize funding, international activities, and impact by WHO, Stop TB, CDC, and various nations, particularly in assessing and addressing priority needs in TB control. In addition to the field assignee at SEARO for TB support for India, DTBE has provided a number of short-term consultancies for specific evaluation exercises and epidemiologic studies. These have included an analysis of seasonal trends of TB diagnosis to determine correction factors for TB drug procurement processes and an evaluation of a public-private sector collaborative project looking at strengthening TB diagnosis and management in the private sector, where 50% of India's TB cases are diagnosed and managed.

CIO: NCHSTP *Start Date: Dec, 2002* **Status:** *ongoing*

WHO Global Salm-Surv conducted eight training courses in FY 03 to help strengthen the skills of microbiologists and epidemiologists in laboratory-based surveillance and outbreak detection and response techniques.

In FY 2000, the U.S. Government launched the Leadership and Investment in Fighting an Epidemic (LIFE) Initiative, which has evolved into the Global AIDS Program (GAP) and is managed by NCHSTP. GAP's objectives include the reduction of HIV transmission through primary prevention of sexual, mother-to-child, and blood-borne HIV transmission; development of programs to improve community- and home-based care and treatment of HIV/AIDS/STI and opportunistic infections; and strengthening the capacity of countries to collect and use surveillance data and to manage national HIV/AIDS programs. Improving TB prevention and control efforts is an important component of the project. DTBE staff members have been actively involved in supporting TB control efforts in several GAP countries, including India. Additionally, DTBE will be providing increased support to GAP for TB prevention, treatment, and care issues in GAP countries identified as part of the Emergency Plan for AIDS Relief (EPAR).

CIO: NCHSTP *Start Date: Jan, 1998* **Status: ongoing**

Vaccine Preventable Diseases

Scientists from NCID's Division of Viral Hepatitis (DVH) have worked with WHO, WHO Regional Offices, and Ministries of Health of numerous countries on several short-term consultancies related to the introduction of hepatitis B vaccine. Ongoing technical support and assistance are being provided to countries to develop routine infant hepatitis B immunization plans, assess hepatitis disease burden, and apply for the Global Alliance for Vaccines and Immunization (GAVI) and Vaccine Fund support. In FY 2003, DVH provided technical assistance to India.

CIO: NCID *Start Date: 2000* **Status: ongoing**

Waterborne Disease

Rural areas in South Asia still lack safe water supplies and sanitary facilities, leading to significant opportunity costs of time spent gathering water and high morbidity from waterborne pathogens. The World Bank funds numerous infrastructure projects to relieve the situation and also is developing state-of-the-art hygiene promotion campaigns to improve health. NCEH's liaison to the World Bank helps develop feasible and useful health monitoring systems that can be integrated into project management. Projects funded by the Bank include rural water supply and sanitation projects in India and Nepal. The NCEH staff member serves as a member of the preparation teams for these projects and is involved in several demonstration projects in these countries to promote better health outcomes through improved hygiene.

CIO: NCEH *Start Date: Jan, 2001* **Status: ongoing**

6. Technology Transfer Activities between the NIH and India

Partnerships Including Technology Licensing

Technology transfer, including licensing, has been part of the biomedical research efforts at the NIH. It is the vehicle through which the outputs of the NIH and the FDA intramural research (in the case of NIH about 10% of its total budget) are transferred to industry to be ultimately developed into medical products to advance human health. The office responsible for managing both the NIH and FDA invention portfolios and to carry out the mandate given by the Congress through its legislative Acts is the Office of Technology Transfer (OTT), located at 6011 Executive Boulevard, Suite 325, Rockville, MD 20852 (www.ott.nih.gov). OTT has been making continuous efforts to expand its activities to countries outside of the United States and in particular to areas of the world where vaccines and therapeutics for devastating infectious diseases are sorely needed. Due to India's tremendous advances in building strong infrastructure and capacity in biomedical research and a biopharmaceutical industry in general, as well as the significant changes in India's IP system and compliance with international standards as a result of India's access to the World Trade Organization (WTO) and its commitment to the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS) that support such an industry, OTT has been making new efforts to utilize IP in India to facilitate new partnerships with Indian's biopharmaceutical companies. OTT has currently fifty-three issued or pending patents in India. Additionally, in the last several years OTT transferred numerous technologies (IP and biological materials) to some of the major vaccine and drug companies in India. Recipients of NIH technologies include companies such as:

- Serum Institute of India Laboratories (SIIL)
- Indian Immunologicals
- Panacea
- Biological E
- Bharat Biotech International
- Shantha Biotechnics
- Ranbaxy Pharmaceuticals
- Biomed (P) Ltd
- Nicholas Priamal India Limited
- Sahajanand Medical Technology

The technologies licensed to these companies include the following:

- Recombinant proteins (called rEPA and rTT) for production of conjugate vaccines against bacterial-caused diseases.
- Novel conjugation method also useful for the efficient preparation of conjugate vaccine (efficient conjugation of carrier protein to bacterial polysaccharide)
- Efficient and high yield process for production of acellular pertussis vaccine
- Rotavirus vaccine based on human bovine reassortant rotavirus strains

At the third quarter of 2007 the vaccine entered Phase III clinical trials with the hope that will become a successful vaccine that will be provided to the African nations.

- Dengue vaccine based on recombinant attenuated Dengue strains
- Vaccine for Varicella-Zoster vaccine based on attenuated virus
- Reagents and vectors useful for the development of HPV vaccine
- DDI – HIV therapeutics
- Methods and compositions for treating alopecia
- Human cell line expressing luciferase reporter gene
- Evaluation of cardiovascular therapy

One partnership through the mechanism of technology transfer is particularly worth noting in this section. In 2005 PATH (Program for Appropriate Technology in Health), a prominent global Non-Governmental Organization (NGO) supported mainly by the Bill and Melinda Gates Foundation, signed a license agreement with OTT (representing the FDA in this case) related to a novel efficient conjugation method for the production of meningitis A vaccine to be used in efforts to combat the devastating epidemic in sub-Saharan Africa. The Meningitis Vaccine Project (MVP),⁴⁷ which was established as a partnership between PATH and the World Health Organization (WHO) is under which this vaccine has been developed. Serum Institute of India Laboratories (SIIL) was selected by PATH with the approval of the NIH to join the MVP project as the sole producer of the vaccine in recognition for the capabilities of this company in vaccine research and manufacturing. The chemical method encompassed in the license agreement was developed at the laboratories of the Food and Drug Administration (FDA) and continues to be improved through a Collaborative Research and Development Agreement (CRADA) between PATH-SIIL and the FDA. The MVP project, with all the complexities of vaccine development, continues to meet the expectations set by the partnership at the initiation of the project. At the third quarter of 2007 the vaccine entered Phase III clinical trials with the hope that will become a successful vaccine that will be provided to the African nations.

Another partnership worth noting is the rotavirus vaccine project. The rotavirus vaccine was developed at Dr. Albert Kapikian's laboratory at the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH and is based on bovine-human reassortant strains. It includes 6 strains of rotavirus and thus has a broad range of reactivity. In 2005 four Indian vaccine manufacturers obtained the rights to develop the vaccine for India and for some countries outside of India. The licensees received all the biological materials required for the vaccine development and are working closely with NIAID scientists at all stages of the commercial development. Most noteworthy is the support of PATH^{6,7} to this project. PATH has been providing some financial support to the project, but is primarily committed to support scale-up procedures and manufacturing of platform reagents through outsourcing.

Interactions between Indian technology management professionals and OTT

The increase in technology transfer activities between the NIH and India in the last several years has led to the creation of special relationship between the NIH Office of Technology Transfer and Indian technology management professionals.

Joint workshops between OTT and Indian technology transfer staff on the topic of “IP Management in Public Private Partnership” took place in the National Centre for Biological Sciences (NCBS) in Bangalore (February 8-10, 2006) and in the Heritage Village, Manesar (February 13-15, 2006). The workshops were organized by NIH/OTT, Indo-U.S. Science and Technology Forum, New Delhi (see above section about the Forum), and the Patent Facilitating Centre (PFC), Technology Information, Forecasting and Assessment Council (TIFAC), Department of Science & Technology (DST),¹⁵ New Delhi. The goal of the workshops was to exchange information and share experiences between the two parties related to technology innovation, management of Intellectual Property and patenting and licensing policies, so as to strengthen the ties between India and the U.S. in the area of technology transfer. Indian participation in each of the workshops included nearly 70 technology managers, scientists, lawyers, and policy officers from the public and private sectors, as well as members from academic institutions. The U.S. delegation included four technology managers from OTT, Dr. Luis Salicrup, Senior Advisor for International Technology Transfer, Dr. Uri Reichman, Chief, Infectious Diseases and Medical Engineering Branch, OTT, Mr. Peter Soukas, a Technology Licensing Specialist at OTT, and Ms. Fatima Sayyid, also a Technology Licensing Specialist at OTT. The workshops were followed with a one day symposium in hotel in New Delhi on February 17, 2006.

Following the workshops and the symposium OTT hosted a number of technology transfer personnel from India under OTT’s international fellowship program. OTT visiting fellows included Dr. Padma Satish, Chief Technical Officer from India Institutes of Technology (IIT) in Bombay, Dr. Sadhana Srivastava, a senior research officer, Intellectual Property Rights Unit of Indian Council of Medical Research (ICMR),¹¹ New Delhi, Mr. Yashawant Dev Panwar from the Patent Facilitating Center (PFC) at TIFAC, Dr. S. Balram from Sree Chitra Tirunal Institute for Medical Sciences and Technology in Kerala State, south India, and Dr. Sukdeb Sinah from the Department of Biotechnology (DBT), Ministry of Science and Technology, New Delhi. These visits and training of the Indian fellows further strengthen the relationship between the two countries in the area of technology transfer.

Indian participation in each of the workshops included nearly 70 technology managers, scientists, lawyers, and policy officers from the public and private sectors, as well as members from academic institutions.

7. The Role of the Indian Department of Biotechnology¹⁴ in U.S.-India Collaborations

The Department of Biotechnology (DBT), under the Ministry of Science and Technology in India was established in 1986 in order to give a new impetus to the development of the field of modern biology and biotechnology in India. In addition to its large variety of activities within India, DBT has recognized the importance of international collaborations. Through the auspices of DBT, collaborations in biomedical research were established with Denmark, Finland, Norway, Korea and Ukraine Germany, UK, Australia, Canada, but by far the most extensive collaborations efforts sponsored by DBT have been with the U.S. Some of the projects supported by DBT have been mentioned in previous sections of this chapter, in particular the Indo-U.S. Vaccine Action Program (VAP), which is partially funded by DBT on the Indian side. At present the projects under implementation under the VAP funding are of rotavirus, hepatitis-C, tuberculosis, RSV and leishmaniasis. The information provided below describing the progress of various joint projects was for the most part derived from DBT Annual Report 2006-2007.

Vaccines Collaborations (under VAP)

Rotavirus: The international partnership for the development of rotavirus vaccine based on the rotaviral diarrhea neonatal vaccine strains 116E and 1321 was mentioned already before, under “Bilateral Agreements between the U.S. and Indian Government” and under the CDC activities in India. The project is making satisfactory progress and is now in phase IIa clinical studies.

Malaria: Under the project implemented at International Centre for Genetic Engineering (ICEB)⁴⁸ and the U.S. Naval Medical Research Center (NMRC)⁴⁹, both through their operation offices in New Delhi, expression of recombinant PvRII (one of the Pvivax Duffy binding proteins) encoding for 38 kD product has been studied. Methods for production of PvRII have been scaled up at the Bharat Biotech International Ltd. in Hyderabad under cGMP conditions. Immunogenicity studies in mice with this malaria candidate vaccine have been successful. Phase-I clinical trials in human have been initiated.

Hepatitis-C: The joint project implemented at Decan College of Medical Sciences & Allied Hospital, Hyderabad and University of Tennessee Health Sciences Center, Memphis, Tennessee focuses on molecular epidemiology of genetic variation in the hyper variable region-1 (HVR-1) sequences of Indian patients and response to interferon therapy.

Tuberculosis: The collaborative study on “High Throughput PCR Assays for Diagnosing Tuberculosis Caused by Mycobacterium Tuberculosis and Mycobacterium Bovis Using Molecular Beacons” at the All India Institute for Medical Sciences (AIIMS), New Delhi, CJILMD, Agra and Public Health Research Institute (PHRI)⁵⁰ Newark, New Jersey supported with an objective to develop reliable devR and hupB-based PCR assays in visual format using

molecular beacons. The beacons were obtained from the U.S. collaborator. This project is currently going through optimization procedures and the studies with clinical samples so far shows promise with respect to specificity and sensitivity of the test.

Leishmania: Studies were conducted at the Institute of Pathology, New Delhi and CBER, FDA, U.S.A on discovery of virulence-related genes in *Leishmania donovani* using genomic microarray. The study has identified the full length ORF of 3 clones and found them to be calpain, NAD/FAD dependent dehydrogenase and a trypanosomatid specific hypothetical protein. Further studies with transcripts of each of these genes implicated their role in disease pathogenesis. Cloning, expression and functional characterization of these genes are underway.

Respiratory Syncytial Virus (RSV) and human Metapneumovirus (hMPV): The first community-based viral Acute Lower Respiratory Tract Infection (ALRI) in India in the past three decades has been conducted at AIIMS, New Delhi and University of Alabama Birmingham School of Medicine, Birmingham, Alabama. The data generated from this joint study will be useful for planning the study of future respiratory virus vaccine for other interventions to reduce the disease due to viral Acute Respiratory Infections (ARIs). Molecular characterization of RSV strains from New Delhi revealed variation in proportion of infections by different RSV genotypes. This is the first study of RSV molecular epidemiology from India, and the first description of the circulation pattern of RSV genotypes in both rural and urban Indian setting.

Group A Streptococcus (GAS): Epidemiological surveillance studies were conducted at Post Graduate Institute of Medical Education and Research (PGIMER)⁵¹ Chandigarh, Christian Medical College (CMC),⁵² Vellore, and NIAID, NIH. At PGIMER, out of a total of 178 group A positive samples of pharyngitis and impetigo,⁵³ emm typing of 111 has been done, emm typing of the rest will be completed in the near future. Anti Steptolysin O and Anti Dnase B will also be continued.

Joint Workshops for Collaborative Projects

In order to have trained personnel to carry out clinical trials and conduct clinical research, DBT, ICMR,¹¹ DCGI (Drug Controller General of India), and U.S. Department of Health and Human Services have organized a series of workshops on clinical trials and clinical research. The goal is to provide state-of-the-art training on clinical research with particular emphasis on clinical trials and the complex requirements necessary for the testing and licensure of drugs, vaccines, diagnostics, and devices for therapeutic and preventative use. The first workshop took place in April 4-6, 2006 at G.S. Medical College & KEM Hospital, Mumbai with the participation of 140 scientists/clinicians. The second workshop on Bioethics in Clinical Research was organized in June 20-22, 2006 in New Delhi, with the participation of more than 100 persons.

Molecular characterization of RSV strains from New Delhi revealed variation in proportion of infections by different RSV genotypes.

This workshop focused on a specific aspect of clinical research related to ethical principles and practices.

Training of Indian Scientists

In 2006-2007 about 300 Indian scientists have been trained in leading institutions in the U.S. for vaccine development and other related technologies. Considerable infrastructure and other facilities have been established under the program in the collaborating India institutions, for advanced R&D.

Joint Working Group (JWG)

The twentieth meeting of Joint Working Group of Indo-U.S. Vaccine Action Program was organized in September 26-27, 2006, to review the progress made under ongoing and completed projects and also to consider new joint projects. A joint Indo-U.S. workshop on “Translational Research” was also organized with this JWG meeting.

Collaboration with the International AIDS Vaccine Initiative (IAVI)⁵⁵

DBT and IAVI, a U.S.- based international organization entered into discussions regarding collaboration in mainly two areas of HIV/AIDS research. The two areas for which proposals were developed and approved are neutralizing antibodies and new antigen design for potential new vaccine candidates.

New initiative: Stanford–India Biodesign International Fellowship in Biomedical Technology Innovation

Stanford University and DBT very recently announced the launch of Stanford-India Biodesign (SIB) fellowship.^{54,56} The goal of the fellowship is to train the next generation of biomedical technology innovators in India. For application to these fellowships the reader is referred to the provided website. The fellowships will start in January 2008. Each fellowship will last two years. Approximately half of the fellows’ time will be spent in New Delhi and the other half at Stanford University. These fellowships will be team based. Fellows will work in a multidisciplinary team joining other innovators with a combination of engineering, medical, and business backgrounds. The team will examine clinical needs within the Indian setting, identifying opportunities for biomedical technology innovation. Working closely with Stanford, AIIMS¹⁹ and Indian Institute of Technology Delhi (IITD)⁵⁷ faculty, the teams will invent, prototype, develop and patent one or more new technologies. Priority will be given to innovations for the medically underserved. In addition to the clinical, business, and engineering faculty at Stanford, AIIMS and IITD, “real-world” experts from the medical technology, legal and venture capital sectors in the U.S. and India will advise and mentor the fellows. Indian citizens with graduate degrees and work experience in engineering, medicine or business will be eligible to compete for the fellowship grants.

E. Conclusion

Collaborations in science and technology have been an enduring feature of the United States-India relationship for more than five decades, and cooperation in the health sciences has been most prominent. Collaborations in the health sciences have intensified since India has committed itself to the standards of TRIPS and thus overhauled its patent law to include product patents (January 2005). This measure and with it, the transition of the Indian biopharmaceutical industry from a generic industry to a more innovative in nature, created incentives for additional organizations from the West to invest in India, and furthermore to collaborate with India in biomedical research. Over the years the U.S. Department of Health and Human Services has played a pivotal role in supporting these collaborations, primarily through its public health agencies such as the NIH and CDC. These collaborative relations intensified in the last few years through the technology transfer activities of the Office of Technology Transfer (OTT) at the NIH. OTT's activities have led in the past few years to the creation of numerous partnerships between the NIH and Indian biotech enterprises, in particular in the area of critical vaccines vital for the developing world. On the Indian side, the Department of Biotechnology under the Ministry of Science and Technology, and in concert with its U.S. counterparts, has taken the lead in supporting and creating such joint collaborations.

This chapter was primarily written to describe the many different opportunities and existing programs available for Indo-U.S. collaborations. The information provided in the chapter regarding the different research funding opportunities, training and scientific exchange opportunities include the relevant websites of specific programs and leading participating institutions. It is hoped this information will be utilized by biomedical scientists both in India and the U.S. In particular it is hoped that U.S.-trained Indian returnees will continue their relationships with their mentoring labs and establish collaborations that will lead to new vaccines, therapeutics and diagnostics for the benefit of public health.

Web Links

1. <http://www.indianembassy.org/newsite/indosci.asp>
2. <http://www.usaid.gov/>
3. <http://www.nih.gov/>
4. <http://www3.niaid.nih.gov/>
5. <http://www.cdc.gov/>
6. <http://www.PATH.org/>
7. <http://www.path.org/vaccineresources/>
8. http://wpgfdn.org/downloads/agencyint_sample.pdf
9. http://www.oar.nih.gov/about/about_oar.htm
10. <http://www.conrad.org/press/May042005.htm>
11. <http://www.icmr.nic.in/>
12. <http://www.nicd.us/>
13. <http://www.nbrc.ac.in/>
14. <http://dbtindia.nic.in/publication/publicmain.html>
15. <http://dst.gov.in/>
16. <http://www.allayurveda.com/discover.htm>
17. <http://www.cmch-vellore.edu/departments/home.asp?did=19>
18. <http://spores.nci.nih.gov/>
19. <http://www.aiims.edu/>
20. <http://www.rti.org/>
21. <http://www.ncaer.org/>
22. <http://www.indiaeducation.ernet.in/insitutions/PROFILE.ASP?no=U01305>
23. <http://www.fic.nih.gov/>
24. http://www.fic.nih.gov/programs/training_grants/icohrta/index.htm
25. http://www.fic.nih.gov/programs/training_grants/itreoh/index.htm
26. http://www.fic.nih.gov/programs/training_grants/mirt/index.htm
27. <http://ncmhd.nih.gov/>
28. http://www.fic.nih.gov/programs/training_grants/aitrp/index.htm
29. http://www.fic.nih.gov/programs/research_grants/firca/index.htm
30. http://www.fic.nih.gov/programs/research_grants/grip/index.htm
31. http://www.fic.nih.gov/programs/research_grants/tobacco/index.htm
32. <http://www.nih.gov/news/pr/aug2002/fic-28.htm>
33. http://www.fic.nih.gov/programs/research_grants/brain_disorder/index.htm
34. http://www.fic.nih.gov/programs/training_grants/irsda.htm
35. http://www.fic.nih.gov/programs/training_grants/genetics.htm
36. http://www.fic.nih.gov/programs/training_grants/itrph/index.htm
37. http://www.fic.nih.gov/programs/training_grants/bioethics/index.htm
38. <http://www.cdc.gov/ncidod/diseases/>
39. www.cdc.gov/nchstp/od/nchstp.html
40. <http://www.cdc.gov/vaccines/>
41. <http://www.cdc.gov/NCEH/>
42. <http://www.atsdr.cdc.gov/>
43. <http://www.cdc.gov/nccdphp/>
44. <http://www.cdc.gov/niosh/>
45. <http://www.epa.gov/>
46. <http://www.phppo.cdc.gov/>
47. <http://www.meningvax.org/>
48. <http://www.icgeb.trieste.it/>
49. <http://www.nmrc.navy.mil/index.htm>
50. <http://www.phri.org/>
51. <http://pgimer.nic.in/>
52. <http://www.cmch-vellore.edu/>
53. <http://www.mayoclinic.com/health/impetigo/DS00464>
54. <http://dbtindia.nic.in/Misc/pdfDoc1.pdf>
55. <http://www.iavi.org/>
56. <http://biodesign.stanford.edu/india>
57. <http://www.iitd.ernet.in/>
58. <http://www.indoustf.org/>
59. <http://www.instp.org/>
60. <http://www.nacoonline.org/>
61. <http://grants.nih.gov/grants/guide/pa-files/PA-07-093.html>
62. <http://grants.nih.gov/grants/guide/notice-files/not99-097.html>
63. <http://www3.niaid.nih.gov/about/organization/dmid/indo>
64. <http://newdelhi.usembassy.gov/pr051507a.html>
65. <http://www.grants.gov/search/search.do?mode=VIEW&oppId=11633>
66. <http://www.trc-chennai.org/>
67. <http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-03-002.html>
68. <http://grants.nih.gov/grants/guide/notice-files/NOT-HD-03-009.html>
69. <http://grants.nih.gov/grants/guide/notice-files/NOT-HD-03-010.html>
70. <http://dbtindia.nic.in/>
71. <http://www.aiims.ac.in/>
72. <http://www.nii.res.in/>
73. <http://www.icmr.nic.in/>
74. <http://www.globalhealth.gov/>
75. <http://www.fic.nih.gov/>
76. <http://grants.nih.gov/grants/guide/pa-files/PAS-04-111.html>
77. <http://grants1.nih.gov/grants/guide/pa-files/PA-07-093.html>
78. <http://www.thehindu.com/2007/09/07/stories/2007090761731500.htm>

About Advances Biopharmaceutical Technology in India

The biopharmaceutical industry in India has grown dramatically over the past few years, and sales have exceeded US\$1.5 billion. This study describes the Indian biopharmaceutical industry, its history, its advantages and opportunities, as well as its challenges and risks. Today, the biopharmaceutical industry in India has brought several protein drugs to market and is developing many more. The next several years will be interesting as India takes its place on the global stage. Biopharmaceutical products have a long history in India, and trace their roots back several thousand years through schools of healing practice. The Indian government is currently working towards developing that experience into a sound biotech industry. The country's objective is to help minimize foreign dependence, especially in high-tech areas. This study describes the industry's history, and the Indian government policies that have helped enable the manufacture of modern biotech products at affordable prices. We discuss the patent factors and history that have shaped the Indian industry, including the industry's reliance on production of outside-of-patent products. As the Indian government continues its efforts to create alliances between private industry and research institutes, the next decade should show a significant growth in the Indian biotech industry, and novel biotech drugs may ultimately dominate. India is expected to emerge as a strong player in the production and sale of biotech products in the coming years, as local consumption rises, and as its local biotech industry takes steps to develop a globally competitive local industry that stands on a foundation of basic research.

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Biospectrum Asia

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