ASSESSMENT OF POTENTIAL COLLABORATIONS IN RESEARCH AND DEVELOPMENT OF NEW REPRODUCTIVE HEALTH TECHNOLOGIES BETWEEN EXISTING USAID–SPONSORED PROGRAMS AND BIOMEDICAL RESEARCH INSTITUTIONS IN RUSSIA

Lee E. Claypool
Laneta J. Dorflinger
Gordon W. Duncan
Vera Grigorieva
Chris S. Robinson

May 2005

Submitted by:
LTG Associates, Inc.
Social & Scientific Systems, Inc.

Submitted to:
The United States Agency for International Development/Russia, Office of Health
Under USAID Contract No. HRN–C–00–00–00007–00

Assessment of Potential Collaborations in Research and Development of New Reproductive Health Technologies Between Existing USAID–Sponsored Programs and Biomedical Research Institutions in Russia was made possible through support provided by the United States Agency for International Development (USAID)/Russia under the terms of Contract Number HRN–C–00–00–00007–00, POPTECH Assignment Number 2005–234. The opinions expressed herein are those of the authors and do not necessarily reflect the views of USAID. This document was formatted but not edited by POPTECH.

ACKNOWLEDGMENTS

This assessment could not have been conducted without the help, dedication, and support of USAID/Moscow. Betsy Brown and Robin Solomon provided invaluable background information on contraceptive, HIV/AIDS, and reproductive health issues in Russian and on the great strides of the Mission in addressing significant health care issues. Olga Frolova, the first contact with the Mission for some of us, provided impeccably thorough and competent logistical support throughout. Michael Stepanov never tired of being our constant companion and master of ceremonies at each of the sites we visited, as well as ensuring that we were appropriately exposed to the cultural aspects of Russia.

Our thanks also for one of our team members, Chris Robinson, who through the CRDF and its local representatives ensured we received adequate premeeting information about each of our sites and about the large, extant interactions between various U.S. Government organizations and the scientific community in Russia. Another team member, Lee Claypool (Office of Population and Reproductive Health, Bureau for Global Health, USAID), kept our energy level high throughout the assignment and contributed more than a fair share of the intellectual input to the final report.

Family Health International deserves special acknowledgement for providing Laneta Dorflinger and Vera Grigorieva and for ensuring that these two major contributors had the time and in-house support necessary to provide their invaluable contributions.

One of us, Gordon Duncan, is also appreciative of the efforts of Larry Smith and Corey Taylor of POPTECH staff who provided contractual and travel arrangements supporting my participation in the project. POPTECH also provided for the final formatting of the report.

ACRONYMS AND ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care
ARTs	Antiretroviral therapies
BII	Bio-Industry Initiative
BTEP	Biotechnology Engagement Program
CA	Cooperating agencies
CD	Compact disc
CDC	Centers for Disease Control and Prevention
CIMET	Center for Integration Medicine and Innovative Technology (U.S. State Department)
CIS	Commonwealth of Independent States
CMCH	Center for Maternal and Child Health
CONRAD	Contraceptive Research and Development Program
CRDF	Civilian Research Development Foundation
CRO	Clinical research organization
CTR	Cooperative threat reduction
CuT	Copper T intrauterine device
DHHS	U.S. Department of Health and Human Services
DIA	Drug Information Association
DNA	Deoxyribonucleic acid
EU–ICH	European Union–International Conference on Harmonization
FDA	U.S. Food and Drug Administration
FHI	Family Health International
FP	Family planning
GCP	Good clinical practice
GDA	Global Development Alliance
GH/PRH	Bureau for Global Health, Office of Population and Reproductive Health, USAID
GLP	Good laboratory practice
GMP	Good manufacturing practice
GOR	Government of Russia
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
ICH	International Conference on Harmonization
ICSSC	International Clinical Studies Support Center
IDU	Intravenous drug user
IPM	International Partnership for Microbicides
IPPF	International Planned Parenthood Federation
IPR	Intellectual property rights
IRB	Institutional review board
ISO	International Organization for Standardization
ISTC	International Science and Technology Center
IUD	Intrauterine device
MMA	Moscow Medical Academy
MOH	Ministry of Health and Social Development, Russia
NGO	Nongovernmental organization
NIH	U.S. National Institutes of Health

NNRTI	Non-nucleoside reverse transcriptase inhibitor
NP	Nonproliferation
Ob/Gyn	Obstetrics and gynecology
OTC	Over the counter
PATH	Program for Appropriate Technology in Health
PCR	Polymerase chain reaction
POPTECH	Population Technical Assistance Project
QA	Quality assurance
QC	Quality control
R&D	Research and development
RAS	Russian Academy of Science
RAPS	Regulatory Affairs Professionals Society
RCMDT	Russian Center for Molecular Diagnostics and Therapy
RFA	Request for application
RFP	Request for proposal
RH	Reproductive health
SANAM	Russian Association for Prevention of Sexually Transmitted Diseases
SOW	Scope of work
SPF	Specific pathogen free
SRIHPB	State Research Institute of Highly Pure Biopreparations, Russia
STD	Sexually transmitted disease
STI	Sexually transmitted infection
TB	Tuberculosis
TEMPO	Center of Modern Medical Technology, Russia
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
U.S.	United States
USAID	United States Agency for International Development
USG	United States Government
VAT	Value added tax
VECTOR	State Research Center of Virology and Biotechnology, Russia
WHO	World Health Organization

CONTENTS

Page

EXECUTIVE SUMMARY i

I. INTRODUCTION 1

II. BACKGROUND 2
RESEARCH, DEVELOPMENT, AND PROVISION OF NEW AND IMPROVED CONTRACEPTIVES 2
Identification and Preclinical Research of New Contraceptive Leads 2
Clinical Testing of New and Improved Contraceptives 2
Acceptability and Introduction Studies 2
Technology-Related Program Research 3
Post-Introduction Surveillance and Epidemiological Studies 3
Quality Assurance of Reproductive Health and Related Technologies 3
MICROBICIDE RESEARCH AND DEVELOPMENT 3
Preclinical Development and Evaluation of Potential Microbicide Leads 4
Formulation and Delivery of Potential Microbicides 4
Clinical Testing of Microbicides 4
Identification of Behavioral Factors and Social Science Issues 4
Provision of Training and Infrastructure 4

III. PURPOSE OF ASSESSMENT 5

IV. ASSESSMENT TEAM 6

V. METHODOLOGY 9

VI. FINDINGS AND RECOMMENDATIONS IN RESPONSE TO THE KEY QUESTIONS 10

Key Question 1. *Are there opportunities in Russia for USAID to advance the research objectives listed in Sections II and III of the SOW? If so, what are the most promising and highest priority opportunities in this area?* 10

Key Question 2. *In particular, are there Russian institutions, e.g., that presently provide clinical health care or conduct clinical research, that have sufficient capacity, experience, and interest to conduct clinical trials of new contraceptives, microbicides, or other reproductive health technologies?* 13

Key Question 3. *What data are available regarding populations in Russia from which potential volunteers could be recruited for clinical trials of new contraceptives, microbicides, or other reproductive health technologies? For what phase of clinical trials, e.g., for safety, expanded safety, or effectiveness in preventing pregnancy or HIV infection, etc., are suitable populations and clinical research sites available? Are there populations and sites that would be suitable to evaluate effectiveness of contraceptives or microbicides in preventing other STIs?* 14

Key Question 4. *If appropriate sites and populations are available, what opportunities, e.g., with which institutions, which trial phases, and which endpoints, etc., could be most productively pursued in the next year? What is the potential for conducting clinical studies on new contraceptives or microbicides, etc., in Russia in the future?* 16

Key Question 5. *What is the regulatory environment for clinical trials as well as other stages of research and development for reproductive health technologies in Russia? For example, what are a) the administrative requirements for approval, conduct, and oversight of research (including local ethical and scientific review, central review, requirements for import of products for clinical research, etc.), b) the extent of ethics and Good Clinical Practice training at various locations, c) the ability to perform research of adequate quality to use for product registration, d) the restrictions on export of preclinical and clinical specimens and/or data for use by collaborating parties? Are there constraints on intellectual property rights that potential collaborators need to be aware of?* 19

Key Question 6. *Are there specific technologies or technical programs in Russia that are linked to commercial channels and capacity that could not only advance research on new contraceptives, microbicides, or other reproductive health technologies, but promote future manufacturing and/or distribution (inside or outside of Russia) of such products as well?* 21

Key Question 7. *Are there particular existing institutions or private sector commercial entities in Russia that could be considered as potential and advantageous partners for manufacturing of new contraceptives, microbicides, or other reproductive health technologies, including their formulation, delivery systems, packaging, or related materials, etc., especially for provision of such products through public sector programs in developing country and low resource settings?* 23

Key Question 8. *Are there opportunities to collaborate on early stage technology research and preclinical product development that would advance reproductive health interests in Russia?* 24

Key Question 9. *What behavioral and social science research, including acceptability of products and services, could be advanced by collaborative efforts and contribute to developing new technology, strengthening service delivery programs, and improved reproductive health?* 32

Key Question 10. *What efforts are needed and possible to build research capacity in any area contributing to improved reproductive health in Russia?* 34

Key Question 11. *What is the current and future potential to use capacity and expertise already existing in Russia to provide technical assistance, training, service delivery, and other contributions to advance reproductive health services and research programs in developing countries, e.g., in Africa?* 36

Key Question 12. *Are there other ways, not included above, that USAID could use the scientific community in Russia to advocate, support, and advance reproductive health research programs?* 37

Key Question 13. *What types of financial and other investments would be needed to pursue any opportunities in the above areas, and by whom?* 37

Key Question 14. *What types of collaborations could be established in the next year and productively implemented in the next 2-5 years?* 39

APPENDICES

A. Scope of Work
B. Organizations Visited and Staff Contacted
C. Notes Regarding Organizations, Persons Visited, Programs, and Potential Products
D. Organization Capabilities
E. Organization Sources of Funds
F. Procedures for Drug Registration
G. Reference Materials

EXECUTIVE SUMMARY

As part of a new five-year development strategy, the United States Agency for International Development (USAID)/Russia is exploring ways of more closely aligning USAID development programs inside Russia with other important and strategic USAID–financed foreign assistance programs, especially those that are relevant and important in biomedical and public health research. The USAID Bureau for Global Health (GH) has a special interest in supporting the research and development of future life-saving health technologies that would be appropriate for public sector programs. USAID/Russia, therefore, requested an assessment to identify how the possibly extensive but underutilized expertise of biomedical and other scientists in Russia could be used more effectively in collaboration with ongoing USAID efforts to address various health objectives, especially those related to the research, development, and provision of new or improved contraceptives, microbicides for HIV prevention, and other reproductive health technologies.

The assessment team included experts in the research and development of reproductive health and microbicide technologies, including a knowledgeable staff person from GH, two medical researchers from a USAID cooperating agency conducting contraceptive and microbicide research and development, an accomplished developer of health products in the public and private sector, and a program manager with experience in public/private collaborations in Russia. The team met with 40 Russian investigators at 20 research institutions in or near Moscow and St. Petersburg during the period March 14–23, 2005.

The assessment team collected preliminary information about which investigators, institutions, and types of research could be most effectively matched with ongoing USAID efforts in this area, as well as ideas for future collaborations. Strategic suggestions on how to pursue these opportunities were developed by the team, although the implementation of any recommendations arising from this effort will largely depend on the future decisions and resource allocations of USAID/Russia. Of necessity, the recommendations for potential collaborations with Russian institutions or parties beyond those that the team was able to meet are more limited.

This assessment report responds as clearly and unambiguously as possible to each of the 14 key questions presented in the scope of work regarding existing research capacities, potential collaborations, and programmatic options. Substantial discussion is provided for each key question along with relevant recommendations. Details and commentary on each of the visits are also included in appendix C. Clearly, the ability of the team to address these key questions was greatly enhanced by the information gained from visiting the Russian investigators and their institutions. Although the team attempted to identify future programmatic, level-of-effort, and relative funding requirements needed to launch new initiatives in these areas, further effort will be necessary to more precisely define these requirements when appropriate.

The assessment report includes 62 recommendations for specific action items to advance the health agenda of USAID/Russia. These suggestions are grouped and summarized as follows:

POLICY

The assessment team suggests that USAID/Russia advocate and otherwise foster a number of policy-related initiatives related to health care and technology in Russia. These include: enhanced coordination and information sharing among all U.S. Government (USG) science and technology programs in Russia to maximize their efficiency and impact; addressing inefficiencies in health care provision and policy per USAID priorities (e.g., in family planning and HIV/AIDS prevention and care); increased support for microbicide research and development from various sources and its coordination with international efforts; changes and clarification of drug regulatory laws in Russia to facilitate product development, clinical testing, and approval; and, support for training and acceptance of higher standards for intellectual property protection in Russia, per international guidelines, with related national policy and judicial reform as needed.

CONTRACEPTIVE CLINICAL RESEARCH

The assessment team identified a number of potential opportunities within Russia to conduct clinical research on contraceptives and reproductive health technologies. Several Russian institutes have significant good clinical practice (GCP) clinical trial experience through collaborations with international pharmaceutical companies, and are well positioned for additional trials with limited staff training. Creating a list of obstetrics/gynecology, sexually transmitted infection (STI), and other infectious disease clinical units within Russia, which have done clinical research previously—in particular with pharmaceutical companies and to GCP standards—would be an important resource and first step for promoting future trials and collaborations. The assessment team identified a number of other specific research ideas to expand contraceptive choice within Russia, including: an introductory trial to offer female sterilization to women who have completed family size; a pilot study of vasectomy to evaluate acceptability; studies of effectiveness, safety, and acceptability of new intrauterine devices (IUDs), such as new hormone-releasing devices; and, clinical trials of other new hormone delivery systems. Adding a Russian obstetrics/gynecology clinical center to one of the multicenter clinical trials supported through the USAID network could be considered.

MICROBICIDE CLINICAL RESEARCH

The high prevalence of sexually transmitted infections, in particular the increasing prevalence of HIV, led the assessment team to identify a number of promising avenues for microbicide research in Russia. While HIV incidence outside the intravenous drug using population is not sufficiently high at present for a HIV prevention trial of a vaginal microbicide, the high prevalence and incidence of non–HIV STIs among various populations provide opportunities for studies of new microbicide drug products or for behavioral interventions. For example, it would be feasible to use non–HIV viral and bacterial STIs as end points in Phase 2–3 studies of microbicide drug candidates. Opportunities may also exist to evaluate vaccine approaches collaboratively with industry to prevent and treat human papilloma virus (HPV), a highly prevalent infection. Trials of oral agents to prevent HIV may be feasible with intravenous drug users, but only if issues of compliance and follow-up for this population are adequately addressed. There are potential opportunities to support the evaluation of a locally manufactured and marked

product, Myramistin, which appears to have broad-spectrum antimicrobial properties. With some training in Phase I methodologies, safety studies conducted to international GCP standards could be immediately funded. Subsequently, effectiveness trials could be considered, involving a number of Russian clinical centers.

BEHAVIORAL RESEARCH

The assessment team identified a number of opportunities for behavioral research on reproductive health technologies, as well as research to better understand and improve risk-reduction and prevention of sexually transmitted infections within Russia. In particular, USAID/Moscow should continue support to the Russian Association for Prevention of Sexually Transmitted Diseases (SANAM) for their important work with high-risk individuals, and consider an increase in funding to allow them to expand their anti–HIV and anti–STI activities. New areas for evaluation would be formative research around acceptability and potential use of female condoms for STI prevention, as well as research on the potential acceptability and use of vaginal microbicides. With regard to contraception, modern reversible method use is comparatively low and use of permanent methods is virtually absent. Acceptability and introduction studies of contraceptives could be done at a range of sites and on a number of programmatic levels. Behavioral research would help to understand barriers to use of contraceptive services. In particular, better understanding provider and user perspectives on male and female sterilization—methods that form a large part of method mix in many mature programs—could expand their use in Russia.

PRODUCT DEVELOPMENT RESEARCH

The assessment team identified a number of opportunities to improve the infrastructure potentially applicable to the identification and development of new contraceptive and microbicide products. Projects include collaborations; workshops, training, and exchange programs; business development programs; public-private sector partnerships; product validation, purity and safety studies; and export opportunities.

TRAINING AND INFRASTRUCTURE DEVELOPMENT

Given the already extensive research capacity and technical expertise among the Russian investigators and institutions visited, appropriately targeted training and infrastructure development could significantly advance health-related priorities in Russia. The assessment team recommends that such capacity building efforts include creating a list serve to periodically inform Russian investigators about opportunities for support or training while highlighting the health and research priorities of USAID/Russia; support for workshops and training specifically on clinical trial design, ethics, methodology, biostatistics, and analysis; promotion or expansion of existing training programs in GCP, good laboratory practice (GLP), and good manufacturing practice (GMP), with sponsorship of trainees selected by USAID/Russia and collaboration with other U.S. Government, contract research, and professional organizations where possible; and, technical assistance in business management and commercialization of health-related product leads, especially for Russian research institutions that are pursuing entrepreneurial opportunities to support their research activities.

The assessment report provides further information and additional details regarding each of these recommendations.

I. INTRODUCTION

As part of a new five-year development strategy, the United States Agency for International Development (USAID)/Russia is exploring ways of more closely aligning USAID development programs inside Russia with other important and strategic USAID–financed foreign assistance programs, especially those that are relevant and important in biomedical and public health research. The USAID research program in the Bureau for Global Health (GH) also has a special interest in supporting the next generation of life-saving health technologies through partnerships between United States and local Russian institutions. To this end, it would be useful to consider how such partnerships could contribute to USAID goals in the research and development (R&D) of reproductive health products including new or improved contraceptive products to prevent or reduce unwanted pregnancies, as well as new products such as microbicides that would prevent or reduce the sexual transmission of HIV and other sexually transmitted infections (STIs). On behalf of USAID/Russia, an assessment of these potential collaborations was undertaken as described below and in the scope of work (appendix A).

II. BACKGROUND

RESEARCH, DEVELOPMENT, AND PROVISION OF NEW AND IMPROVED CONTRACEPTIVES

For more than two decades USAID has been recognized as a global leader in the field of contraceptive research and development. USAID has played an important role in the development, testing, and regulatory approval of many contraceptive products available in the market today, including low-dose oral contraceptives, the CuT 380A intrauterine device (IUD), Norplant and Jadelle implants, novel female barriers, and other methods of family planning (FP). In addition, USAID has played a key role in improving the provision and use of these and other methods (such as Depo-Provera) throughout the world. USAID also plays a unique leadership role in ensuring the high quality of contraceptives that it provides worldwide. Family planning (FP) and reproductive health (RH) programs face many new questions and challenges during the next decade. The demand for safe, effective, acceptable, and affordable contraceptives and disease prevention technologies will continue to grow as millions more young women and men throughout the world reach reproductive age.

USAID supports a broad portfolio of research activities which cover the continuum from the conception of an idea or approach through the use of the final technology by a client in a family planning and reproductive health program. These activities include the following.

Identification and Preclinical Research of New Contraceptive Leads

The increased knowledge of reproductive biology and advances in molecular biology and other disciplines are being used to identify new contraceptive product leads. Some currently available methods may also need to be modified and improved to make them safer as more is learned about the risks associated with their long-term use. In some cases, it may also be possible to improve product effectiveness through better formulation technology.

Clinical Testing of New and Improved Contraceptives

Clinical trials with appropriate volunteers are needed for all new contraceptive products to assess their safety, acceptability, and effectiveness in preventing or reducing the risk of pregnancy.

Acceptability and Introduction Studies

No single method is likely to meet the contraceptive and reproductive health needs of every woman or man. In addition to safety and effectiveness, the duration of action, availability, convenience, stage of reproductive life, and affordability also play a role in determining the technologies that are made available and that an individual or couple selects and uses. Contraceptive and other reproductive health decisions are also strongly affected by culture, public health and health care policies, and service delivery characteristics in the country where the individual or couple lives.

Technology-Related Program Research

Additional training and technical support are needed to strengthen service programs and enable them to provide contraceptive and disease prevention methods to the most people, in the most appropriate ways, and with limited resources, given the health, social contexts, and risk factors of the clients. Many service programs need to address questions such as: How can family planning programs provide prevention, diagnosis and/or treatment for STIs? Conversely, how can HIV/AIDS programs provide appropriate contraception? How can service providers best address the reproductive health needs of various target groups, prevent unsafe abortion, and mitigate other chronic health conditions that affect the quality of life of many women and men? Cost and sustainability research is also needed to identify what program options are possible, define what resources are needed, and inform subsequent programmatic decisions.

Post-Introduction Surveillance and Epidemiological Studies

Questions of interest address issues such as: How do contraceptives affect the acquisition and progression of HIV/AIDS? What is the impact of different hormonal contraceptives on such subjects as reproductive cancers, bone density, and other health parameters? Assurances that contraceptive methods are safe must be made on the basis of sound research. Efforts are also needed to define and better meet the contraceptive and other reproductive health needs of groups that have traditionally received less attention from family planning programs. These groups may need to be reached through nontraditional approaches. Pregnancy, unsafe abortion, and a variety of STIs are among the many reproductive health risks that confront growing numbers of young people in many countries. In addition, reproductive health technologies may affect young people differently than adults, and the acceptability and affordability of these technologies may also differ.

Quality Assurance of Reproductive Health and Related Technologies

In addition to developing and improving new reproductive health technologies, it is critical that the quality of these technologies is monitored worldwide to meet high international standards. USAID has supported the development of facilities and techniques to evaluate the quality of contraceptive products and has helped define the international standards used for this testing. Research is also needed to develop quality assurance methods for other reproductive health products such as STI test kits, antiretroviral therapies (ARTs), and other diagnostic and therapeutic products. There is a need to develop simple quality assurance (QA) tests that can be performed at developing country sites inexpensively and efficiently. This involves building local capacity for monitoring product quality, as well as providing the appropriate technologies for these programs.

MICROBICIDE RESEARCH AND DEVELOPMENT

Because current strategies for preventing sexual transmission of HIV, such as condom use by the male partner, are often not available options for many women, USAID is actively developing vaginal microbicides as a female-controlled chemical barrier to HIV. For more than a decade, USAID has supported the biomedical and behavioral research that is needed for the successful development of such products. These efforts have

yielded several promising candidates, some of which are now or soon beginning the final stages of clinical testing in international trials for their safety, acceptability, and effectiveness in preventing or decreasing sexual HIV transmission.

USAID has collaborated with the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) to develop the U.S. Government Strategic Plan for Microbicides. The objectives of this plan and USAID–sponsored activities include the topics that follow.

Preclinical Development and Evaluation of Potential Microbicide Leads

A broad spectrum of early stage research is needed to support the discovery, characterization, and subsequent development of potential new active agents for use in microbicides.

Formulation and Delivery of Potential Microbicides

Given the identification of promising new active agents, it is essential to develop and assess safe, acceptable, and effective formulations and modes of delivery for microbicides, applying knowledge from the chemical, pharmaceutical, physical, bioengineering, and social sciences.

Clinical Testing of Microbicides

Extensive clinical trials will be needed with appropriately selected volunteers to assess the clinical safety, acceptability, and effectiveness of new microbicides in reducing the transmission of HIV and other STIs (and preventing pregnancy for products that are also contraceptive) in developing countries and the United States.

Identification of Behavioral Factors and Social Science Issues

Behavioral and sociological research is needed to enhance microbicide development and testing, and to better understand factors that will affect future microbicide use and acceptability in developing countries.

Provision of Training and Infrastructure

Significant capacity building is needed to establish, maintain, and strengthen the appropriate training and infrastructure needed to conduct microbicide research internationally and to accelerate future access to microbicides in diverse populations and settings.

III. PURPOSE OF ASSESSMENT

The purpose of this assessment was to have a team of relevant experts examine the feasibility of more closely and effectively linking the USAID/Russia health and infectious disease programs, the USAID Bureau for Global Health programs in reproductive health research (especially contraceptive and microbicide research and development), and the existing research expertise and capacity of Russian scientists and institutions. The assessment sought to identify the specific means by which ongoing USAID efforts to address various reproductive health objectives (especially those that are described above and appear in Section II and III of the scope of work) could be more effectively achieved in collaboration with biomedical and other scientists in Russia. The assessment report presents preliminary information on which investigators, institutions, and types of research could be most effectively matched with the ongoing USAID efforts in this area, identifies strategic criteria for additional collaborative opportunities between USAID and Russian scientists and institutions in the future, and suggests possible actions that could be undertaken by USAID to advance these collaborations in both the near and long term. This assessment primarily collected information, ideas, and suggestions. The implementation of any recommendations arising from this effort will depend on future decisions and resource allocations.

IV. ASSESSMENT TEAM

The assessment team included experts in the research and development of reproductive health and microbicide technologies. It included

- a USAID staff person familiar with the contraceptive and microbicide research and development programs sponsored by the Bureau for Global Health, as well as by other U.S. Government agencies and other donors or sponsors;

- medical researchers currently working with existing USAID–funded contraceptive and microbicide projects to develop new clinical research sites and to implement clinical studies to evaluate safety and effectiveness of current product leads at those sites;

- an experienced developer of reproductive health products in the private and public sectors; and

- a program manager with experience in promoting public/private sector collaborations in Russia.

The technical expertise represented in the composition of the team intentionally emphasized the technical assessments needed to address the key questions focusing on clinical trials research, but it was also intended that assessment team members address each of the key questions as thoroughly as possible within the scope of their expertise. This focused the greatest technical expertise of the assessment team on the potential for conducting contraceptive and microbicide clinical trials in Russia, since such trials are a great programmatic and technical need in the next year (especially for microbicides), while collecting and evaluating information on other opportunities to support research on reproductive health technology and services as well. It was also intended to assess the potential to collaborate on advancing promising product leads that are still at the preclinical stage of development, as well as later stage needs such as capacity for manufacturing, packaging, and distribution of products.

The following individuals were on the assessment team.

Lee E. Claypool, Ph.D. Dr. Claypool is a biologist in the Research, Technology, and Utilization Division of the Office of Population and Reproductive Health in the Bureau for Global Health at the U.S. Agency for International Development. He is the Team Leader for Biomedical Research and provides technical leadership in the research and development of microbicides for the prevention of HIV and other sexually transmitted diseases as well as new contraceptive products. This involves program development, management, and coordination to advance state-of-the-art technologies, expand access to quality services, promote healthful behaviors, broaden contraceptive availability and choice, and strengthen policies and systems to address reproductive health needs. Dr. Claypool was formerly on the faculty of the Eastern Virginia Medical School in the Department of Obstetrics and Gynecology and was Research Coordinator for the Contraceptive Research and Development Program.

Laneta J. Dorflinger, Ph.D. Dr. Dorflinger has more than 20 years experience in the fields of contraceptive technology, international family planning and microbicide development. She currently directs and provides leadership to a global clinical research program that evaluates new and existing methods of contraception and microbicides. Since joining Family Health International (FHI) in 1991, she has held several leadership positions including vice president of research and development, director of clinical trials, and director of regulatory affairs and quality assurance. She managed the conduct of clinical trials, oversaw development of clinical protocols and monitoring and evaluation plans, established policies on regulatory affairs and quality assurance, oversaw regulatory submissions to the FDA, and interacted closely with federal regulators. Prior to joining FHI, Dr. Dorflinger worked for seven years in the research division of the Office of Population at USAID, where she managed multiple projects related to contraceptive development, introduction, and evaluation, and provided scientific and technical guidance to the division. Her work has taken her to numerous developing countries to monitor ongoing projects and to serve interim roles at local USAID Missions.

Gordon W. Duncan, Ph.D. Dr. Duncan has more than 40 years experience with major United States-based and international pharmaceutical companies and with two multinational nonprofit research and development institutions that have a developing country orientation. He conducted fundamental endocrine research and discovered and developed medically unique drugs and devices for reproductive and family planning applications. He structured, managed and led multidisciplinary, multinational research and drug development teams. He adapted and introduced medical products for use in developing countries; consulted for, negotiated with, and coordinated programs with government, academic and industrial institutions. He designed and implemented domestic and global research and development programs and policies. Additionally he has been a member of senior management of four emerging biopharmaceutical companies. Dr. Duncan has significant experience in working with private-public sector partnerships.

Vera Grigorieva, M.D. Dr. Grigorieva is an obstetrician/gynecologist with 11 years of clinical and research experience in obstetrics, gynecology and family planning. She currently is serving as a scientist in the Clinical Research Department at Family Health International, where her responsibilities include but are not limited to designing and managing implementation of clinical trials in the areas of reproductive health and HIV/STI prevention. Her current assignment is as a project leader of a Phase III multicenter microbicide trial conducted in Nigeria. Dr. Grigorieva has extensive experience in training of health care professionals and providing technical assistance in development of guidelines, manuals, and training materials in the area of reproductive health. Dr. Grigorieva has provided consultancy services to many international agencies and donors working in the area of reproductive health.

Chris Robinson, MPH. Mr. Robinson received his training in molecular epidemiology and researched intestinal parasite prevalence and detection methods in Costa Rica and the United States Since 2001, he has worked in biological research program management in Russia, Georgia, Kazakhstan, and Uzbekistan. His work has included assessing institutional capabilities, identifying opportunities for collaborations with United States researchers, linking United States and Commonwealth of Independent States (CIS) research teams, and planning and implementation support for research projects funded by

several U.S. Government agencies. He has accompanied dozens of teams of U.S. researchers to CIS research centers and CIS researchers to U.S. research centers.

Michael V. Stepanov, Project Management Specialist, USAID/Moscow. Mr. Stepanov accompanied the assessment team on its visits and provided critical liaison functions between team members and institution representatives.

V. METHODOLOGY

The visit of the assessment team to Russia occurred March 14–23, 2005, and included visits to 20 relevant research facilities located in or near Moscow as well as in or near St. Petersburg (please see appendix B for names of facilities, persons met, and contact information).

The Civilian Research and Development Foundation (CRDF), having already worked extensively with various U.S. Government entities and scientists at Russian institutions to establish other joint research efforts in the prevention and treatment of HIV/AIDS, sexually transmitted diseases (STDs), tuberculosis, hepatitis, and other diseases, was instrumental in identifying the individual investigators and institutions that were useful for the assessment team to visit. Many staff at the USAID/Russia Mission in Moscow contributed to providing background information and briefings to the team.

USAID/Russia requested that the assessment team's report contain recommendations and strategic priorities for research in reproductive health technology and respond as clearly and unambiguously as possible to the key questions in the scope of work, presented in appendix A. To the extent possible, the final report was also to suggest future programmatic, staffing (level of effort), and funding requirements needed to launch credible new initiatives in this area, and identify the specific Russian institutions and existing USAID cooperating agencies (CAs) with which promising partnerships can be established. Because of limitations in time, the team was only able to meet with a limited number of Russian organizations in Moscow and St. Petersburg regions, so the team's ability to recommend potential collaborations beyond those organizations cannot be comprehensive. Other information included in the report was determined in consultation with USAID/Russia staff before and during the assessment. The structure and format of the report was proposed by the assessment team and an outline for the report was approved by USAID/Russia staff at the beginning of the assessment.

Discussions and presentations with USAID/Russia staff and consultants and the additional background materials they provided on health issues within Russia were of great assistance to assessment team members in focusing their awareness on the issues and were invaluable in subsequent discussions with staff at the organizations visited.

The following findings and recommendations are endorsed unanimously by the assessment team; any stylistic differences throughout Section VI reflect only the multiple contributors to the writing of the report.

VI. FINDINGS AND RECOMMENDATIONS IN RESPONSE TO THE KEY QUESTIONS

Following are responses to the fourteen key questions with supporting recommendations and strategic priorities for research in reproductive health technology in Russia. The key questions are those presented in the scope of work (please see appendix A).

> Key Question 1. *Are there opportunities in Russia for USAID to advance the research objectives listed in Sections II and III of the SOW? If so, what are the most promising and highest priority opportunities in this area?*

Based on the assessment team's visits with Russian scientists and other information acquired during this effort, the following comments are made in reference to each of the research objectives described in Sections II and III in the scope of work (appendix A) regarding the research and development of new or improved family planning products as well as vaginal microbicides for the prevention of sexually transmitted HIV infection. Where possible, the responses to the other key questions (below) include specific examples of how research objectives in these and other areas of health research could be advanced by USAID in Russia, along with a more complete discussion of critical related issues.

For family planning products, as noted in the scope of work, USAID support for the research and development of new or improved products includes a broad portfolio of activities covering the continuum from inception of a new idea or approach through the use of the final technology by a client in a family planning and reproductive health program.

In regard to the "***Identification and Preclinical Research of New Contraceptive Leads,***" the assessment team was able to meet with a variety of scientists working in fields that could potentially contribute to this objective. These fields included molecular biology, immunology, protein chemistry, pharmacology, and toxicology, as well as the more clinical and therapeutically focused disciplines. It was very evident that the appropriate expertise and capacity to contribute to new contraceptive leads is present, but there was no evidence that research related to contraceptive research and development was fostered by any defined program at the national or institute level or was the personal goal of any of the individual Russian scientists that the assessment team met or heard about. The potential for Russian scientists to contribute in this area appears, therefore, to be substantial but completely undeveloped at this time. Targeted efforts to inform Russian scientists about opportunities in this area funded by existing sources outside of Russia, or by new programs inside Russia, could contribute to changing this situation. Any of a range of efforts, from facilitating new partnerships to developing significant new funding programs, would be appropriate in this regard.

For "***Clinical Testing of New and Improved Contraceptives,***" the assessment team met with a number of clinicians and researchers in obstetrics and gynecology, and to a limited extent infectious diseases, who could become collaborators and contribute to this objective. The team found that there is clearly extensive relevant clinical care expertise, as well as selected expertise in conducting clinical trials of contraceptive methods. In

contrast, despite clinical expertise in studies of therapies to treat STIs, there is minimal experience in conducting clinical trials of microbicide (prevention) products. In addition, experience in conducting clinical trials among the institutes visited by the assessment team largely involves collaborations with multinational organizations as part of multicenter clinical trials, as opposed to institute staff leading the design and implementation of original contraceptive research. Most of the institutes visited had access to potential populations of trial volunteers to assess the safety, acceptability, and effectiveness of new products in preventing or reducing the risk of pregnancy. There are, however, some specific and unique logistical and regulatory hurdles for conducting such studies in Russia, both for products developed inside Russia and abroad, that would have to be addressed and are discussed below.

Available statistics for measures of reproductive health in Russia indicate that "***Acceptability and Introduction Studies***" for new contraceptive products, or for those which are not currently available or prevalent in Russia, could be very appropriate and productive in terms of measurable health outcomes. The prevalence of modern contraceptive method use is remarkably low in Russia and new efforts to introduce and promote the modern methods already commonly available outside of Russia should be given a very high priority. Well-trained medical personnel are available in large numbers and the provision of care is generally well organized, although marginalized populations, including transients, ethnic minorities, intravenous drug users (IDUs), and other persons, have less effective access to care, as elsewhere in the world. The assessment team was able to visit several clinics that specifically target services to marginalized populations and it was clear that these are unique and pioneering efforts in Russia. Clearly, all postpregnancy women are an important focus of work in this area Acceptability and introduction studies could, therefore, be done at a range of sites and on a number of programmatic levels, but are not currently identified as a focus of activities for any of the health professionals visited by the assessment team.

Regarding "***Technology-Related Program Research***" in Russia and in developing countries, the assessment team did not meet individuals specifically trained in this discipline and heard of only one initiative (of national or institutional programs) to support research on how to improve the provision of services (a collaboration with the Swedish government related to improving STI services in the Leningradskaya Oblast). The need to improve services, however, was readily identified by a number of the clinicians with whom the assessment team met, and a variety of problems and possible solutions that could be usefully investigated by operations research were discussed. Some of these problems involved integration of services (e.g., diagnosis of HIV infection and referral for treatment) and involved difficult policy issues as well (e.g., provision of HIV treatment only in defined home provinces that were inaccessible for transient persons). Addressing inefficiencies in health care systems would be an extremely broad undertaking in any country, but there are priorities, such as those defined by USAID for the integration of family planning programs with HIV prevention and treatment programs, that continue to be highly appropriate for support in Russia, along with other high priority programs such as tuberculosis prevention and treatment. Research is clearly needed to identify program options, estimate their cost and sustainability, and inform changes in policies.

"***Post-Introduction Surveillance and Epidemiological Studies***" might be technically feasible in Russia to address many issues regarding contraceptive use, impact, and safety in the broader population. A compelling and immediate need, however, may be to define and better meet the contraceptive and other reproductive health needs of the populations that are at high risk and are marginalized in their access to health. Since these groups may need to be reached through nontraditional approaches, surveillance and epidemiological studies may be especially informative to document and improve the effectiveness of these programs.

The assessment team visited facilities with considerable capacity to do state-of-the-art chemical analyses that are being used to assess the safety and equivalence of the many generic drugs being developed or introduced in Russia. This testing already meets or could be upgraded to meet international standards suitable for the "***Quality Assurance of Reproductive Health and Related Technologies.***" The capacity for this type of QA monitoring could be even more critical if the production of generic products expands in Russia and export of these products to other countries is increased. Although the scientists the assessment team met were not pursuing contraceptive research and development, they were working on new STI test kits, antiretroviral therapies, and other diagnostic and therapeutic products. In some cases they were already marketing these products in Russia as well as other Commonwealth of Independent States (CIS) countries. Some of these products might have useful applications in developing countries in the future, although the technical details of their performance and related cost factors would have to be evaluated further, and the required product review, approval, and registration would be needed from the appropriate national regulatory agencies in the destination countries. Moreover, apparently in part as a result of past programs in biological warfare and related safety issues, there is very specific expertise in Russia for the detection of biological contamination. This expertise could be very useful for monitoring the purity and safety of many medical products, possibly including disease-preventive and therapeutic products, or blood and other tissue products, as well as the effectiveness of procedures such as for sterilization or purification. The possibility of transferring such capabilities, including expertise and equipment, to developing country settings was not sufficiently addressed for particular comments, but could be investigated further by USAID/Russia when appropriate.

Many of the key factors regarding the capacity of Russian scientists for research and development of microbicides that would prevent sexually transmitted HIV and other STIs are similar to those for family planning and other reproductive health products, and were discussed with Russian investigators whenever appropriate.

Discussions regarding the "***Preclinical Development and Evaluation of Potential Microbicide Leads***" identified research groups that were interested in the broad spectrum of early stage research needed to support the discovery, characterization, and subsequent development of potential new active agents for use in microbicides This particularly includes the collaborating researchers at the Ivanovsky Institute of Virology and the Research Institute of Immunology, who already have some capacity to screen potential agents for anti–HIV activity in vitro and were very interested in establishing new ex vivo tissue models for this purpose in their laboratory. An exchange program supporting travel abroad for such collaborative research could be very useful. These investigators, as well as others that the assessment team was not able to meet (such as the microbicide

research group from VECTOR) participated in the Microbicides 2004 Conference in London (April 2004) as well as a Conference on Microbicide Research and Development in Russia that was subsequently held in St. Petersburg (November 2004). There is interest in holding another conference in Russia in 2005, and the Microbicides 2006 Conference is already being planned in Cape Town, South Africa. Travel support from USAID or other sources for Russian investigators to attend these and similar meetings, and to support future research collaborations, could be very productive for their research. It was not evident to the assessment team that any of these investigators have clearly promising lead agents at this time, but some of the candidates, such as the ascorbigen agent described at the G. Gauze State Institute for New Antibiotics, merit more evaluation. A number of Russian investigators are also working with novel antimicrobial peptides, which may have very important medical applications. Peptides, however, are regarded by many in the field as too expensive to manufacture for use as a microbicide product that would ideally approach the cost of a condom. Smaller peptides, such as the 12 amino acid lead at the State Research Institute of Highly Pure Biopreparations, however, would not be as expensive as the larger ones. Russian investigators who clearly had expertise in the "***Formulation and Delivery of Potential Microbicides***" were not met by the assessment team, although some of the investigators that were met expressed an interest in this subject (e.g., at the Ivanovsky Institute of Virology), and other investigators described products or interests at their institutes that involved other targeted drug delivery technology (such as for oncology and tuberculosis therapy at the Research Center of Molecular Diagnostics and Therapy). The InfaMed Company also manufactures Myramistin (broad-spectrum antimicrobial) products in a variety of formulations, although there was no opportunity to discuss how these formulations had been developed and tested.

The potential capacity in Russia for "***Clinical Testing of Microbicides***" is discussed more fully in response to key questions 2 and 3 below. The logistical and regulatory constraints are largely similar to those for the clinical testing of contraceptive products. The existing clinical expertise and facilities suggest that microbicide safety and acceptability studies would be feasible in Russia. As noted elsewhere, however, it is not possible to evaluate the effectiveness of vaginal microbicides in preventing sexual transmission of HIV unless there are sufficiently large populations of women who have a very high risk of infection due exclusively to exposure through vaginal intercourse; such populations may not be available in sufficient numbers for enrollment in clinical trials in Russia. Another possibility, however, would be to evaluate the effectiveness of a microbicide in reducing the transmission of other viral and bacterial STIs. Some "***Provision of Training and Infrastructure***" could be appropriate with USAID support (either through bilateral or core funds) if one of these clinical trial options could be developed further. Specific expertise in the "***Identification of Behavioral Factors and Social Science Issues,***" needed to enhance microbicide development and testing and to better understand the factors that will affect future microbicide use and acceptability, was not evident among the investigators that the assessment team met or heard about.

Key Question 2. *In particular, are there Russian institutions, e.g., that presently provide clinical health care or conduct clinical research, that have sufficient capacity, experience, and interest to conduct clinical trials of new contraceptives, microbicides, or other reproductive health technologies?*

Russia has considerable relevant clinical practice experience and clinical trial capacity. The assessment team visited several medical institutions in two cities: Moscow and St. Petersburg. (We understand that there are 47 medical schools in Russia, however, our ability to provide an assessment of the institutional capabilities outside of those we visited is limited.) The institutes visited reported experience in clinical trials in a broad range of therapeutic areas. Several of the organizations have participated in studies for United States and European pharmaceutical companies facilitated by the use of clinical research organizations (CROs), which is a positive sign for future USAID activity. While the assessment team was unable to fully assess the capabilities of these institutes, their participation in international studies indicates compliance with international good clinical practices (GCP) standards, at least among those staff who were involved in these trials. Further research by the assessment team indicates that there are many sites in Russia other than those we visited that participate in international, multicenter clinical trials.

To conduct clinical trials in Russia, an institution must have a special license from the Government of Russia. We believe that only six institutions currently have these licenses in the area of obstetrics/gynecology, including several of the institutes we visited. These institutes, especially those that have international trials experience in other therapeutic areas, seem best positioned to attain international GCP standards in reproductive health clinical trials rapidly.

The assessment team did not fully analyze the kind and extent of resources that would be required to support and expand capacity of an institute to participate in international-standard reproductive health clinical trials. For staff that have no prior experience, a large amount of GCP training would be required prior to initiation of trials, and ongoing monitoring would be essential. Even institutes that already participate in international trials cited a need for more training. In addition, we found no evidence of clinical trials designed and implemented by the institutes without outside participation that would meet the rigors of international standards. They would need further training on a broad spectrum of research processes, as addressed elsewhere in this report

From a review of various web sites, it appears that clinical research collaborations with a number of United States and European pharmaceutical companies are strong and are being conducted in a variety of major Russian medical centers across the majority of therapeutic areas. One suggested action is to develop a list of obstetrics/gynecology and STI and other infectious disease clinical units within institutes or organizations in major Russian cities, and determine which have licenses and which have done clinical research previously, in particular with pharmaceutical companies and to GCP standards. Such a list could facilitate partnering and project development using U.S. Government or other public sector support.

> Key Question 3. *What data are available regarding populations in Russia from which potential volunteers could be recruited for clinical trials of new contraceptives, microbicides, or other reproductive health technologies? For what phase of clinical trials, e.g., for safety, expanded safety, or effectiveness in preventing pregnancy or HIV infection, etc., are suitable populations and clinical research sites available? Are there populations and sites that would be suitable*

to evaluate effectiveness of contraceptives or microbicides in preventing other STIs?

The conduct of clinical trials requires access to sufficient numbers of individuals who meet inclusion/exclusion criteria of a protocol and who would be motivated to participate. During our visits, the assessment team had limited ability to assess the potential for participant availability by site, and was not given detailed information regarding specific characteristics of clinic populations or clinic flow at the sites visited. This latter would need to be established before committing to any clinical trial. However, at some of the sites, we did receive general information about clinic patient volumes. In addition, a site's past participation in relevant clinical trials, as well as past performance on these trials, is an indication of the potential for successful conduct of studies in the future (please see appendix C, Notes Regarding Organizations, Persons Visited, Programs, and Potential Products). Institutes have been successfully involved in international multicenter clinical trials of contraceptive methods. Data from such studies are used by pharmaceutical companies to support introduction of these new products into Russia (e.g., the Evra patch, Implanon implant). In two sites (Pavlov University in St. Petersburg and the Research Center for Obstetrics and Gynecology and Perinatology in Moscow), we heard reports of very rapid enrollment rates into clinical trials.

The assessment team received demographic and epidemiologic information on Russian populations (including rates of abortions, use of modern contraceptive methods, prevalence of STIs, most common means of HIV transmission, rates of other infectious diseases, etc.) that also helped us to respond to this question. There is a high degree of morbidity within Russia and a high prevalence/incidence of communicable diseases beyond STIs, including tuberculosis and hepatitis. Access to health care, in particular care for STIs, is limited for many individuals in Russia, especially from high-risk groups (e.g., migrants) because free services are only provided within the area/region in which one is registered. For many individuals, access to certain types of health care may be temporarily improved through participation in clinical trials. Assuming the benefits of the trial can balance any undue incentive, there could be a large population willing to join clinical trials to evaluate various health technologies.

All phases of clinical trials for contraception could potentially be done in populations available in Russia. IUDs are particularly popular in Russia, constituting more than 60 percent of modern method use in 2003. As such, effectiveness studies of new IUDs, including hormone-releasing devices, would be highly feasible. Hormonal contraception constituted about 37 percent of modern method use in 2003. We were told that use of hormonal methods may be declining at present because of cost. However, three clinical centers we visited had participated in multicenter trials of new hormonal methods including implants, vaginal rings and a hormonal patch, and successfully enrolled patients in these studies quickly. This indicates a capacity that could be tapped for other similar trials. Use of barrier methods, other than condoms, appears limited and we did not specifically address interest in trials of methods such as new female condoms. However, given the high rates of sexually transmitted infections among some of the population, interest in conducting trials of such methods should be encouraged. Voluntary sterilization, both male and female, is very limited across Russia, so trials of new approaches such as nonsurgical female sterilization or vasectomy would probably not be feasible in the near term. On the other hand, one research opportunity would be to

explore the reason for resistance, from both a provider and user perspective, to sterilization and to determine whether expanded services might be feasible (see key question 9 below related to behavioral research).

All phases of clinical trials for products to prevent or treat non–HIV STIs (e.g., gonorrhea, chlamydia, and herpes,) could potentially be done in Russian populations as well. In contrast to HIV, the prevalence of bacterial STIs as well as herpes and human papilloma virus (HPV) is high among many of the clinic populations (STI sites as well as family planning clinics). For example, following the cure of bacterial STIs, reinfection rates were reported to be quite high among the high-risk population attending the Russian Association for Prevention of Sexually Transmitted Diseases (SANAM) clinic. This would make it feasible to conduct trials of microbicides with these STIs as outcomes, or to evaluate new therapeutic products. In contrast, Phase 3 clinical trials of vaginal products for HIV prevention do not seem feasible, given that the main mode of transmission in Russia at present is via intravenous drug users (IDUs) and that the incidence is (fortunately) not sufficient to conduct reasonable size trials among the non–IDU population. Trials of oral agents to prevent HIV may be feasible with IDUs if issues of compliance and follow-up for this population could be sufficiently addressed. In addition, the epidemiology of HIV transmission is beginning to change in Russia and an estimated 40 percent of incident cases last year were through heterosexual transmission to young women. As such, it may be possible in the future to consider sites in Russia for HIV prevention trials. This situation should be monitored.

> Key Question 4. *If appropriate sites and populations are available, what opportunities, e.g., with which institutions, which trial phases, and which endpoints, etc., could be most productively pursued in the next year? What is the potential for conducting clinical studies on new contraceptives or microbicides, etc., in Russia in the future?*

Based on the snapshot of clinical institutes visited, there would appear to be many opportunities to conduct research on new contraceptives within Russia. These clinical institutions have highly trained obstetricians and gynecologists, and access to reasonable numbers of potential participants. Some of these centers have active collaborations with the United States and European pharmaceutical industry, and have conducted trials for product introduction within Russia. Since Russian funding for clinical research is limited or nonexistent, there is great interest in identifying U.S. Government support and collaborations.

Contraception trials. There is a substantial unmet need for contraception—only 23 percent of women of reproductive age in Russia use modern methods of contraception. Abortion continues to be one of the main methods of fertility regulation, and presents a serious socioeconomic and public health problem in Russia. Indeed, we were told that 'preventing abortion' is a new term being used for contraception. As indicated in the answers to key questions 2 and 3, there is both an interest and potential participant populations for conducting effectiveness trials of new contraceptive products in Russia. New contraceptives could be tested within the format of Phase 1 and 2 trials in all the clinical institutes visited. In addition, all of the institutes could potentially serve as a site in a multicenter Phase 3 trial evaluating contraceptive effectiveness. Post-marketing Phase 4 or introductory trials can be conducted at all clinical sites, and some of the

centers we visited had collaborations in the broader surrounding community that would expand their reach for introductory trials. Any contraceptive clinical trials conducted in Russia will also provide great benefits due to the affiliated education provided within a clinical trial setting to both health professionals and participants.

The following are recommended:

- In the next year, adding a Russian obstetrics/gynecology clinical center to one of the multicenter clinical trials supported through the USAID network could be considered (e.g., for vaginal rings, female condoms).

- Given method mix has little to no female sterilization, an introductory trial to offer female sterilization to women with completed family size could be supported.

- With little or no male sterilization throughout Russia, a pilot trial to offer vasectomy could be supported and coupled to behavioral research to better understand potential barriers to its broader use (see key question 9).

Microbicides. As indicated in the answer to key question 3, microbicide clinical trials in support of HIV efficacy determinations (in contrast to product acceptability trials) may be difficult to conduct because of inadequate subject numbers in appropriate target populations. IDUs, although numerous, are not a suitable population for efficacy trials of vaginal products. They are historically a very difficult population to work with and present additional challenges for participant recruitment. It may be possible to evaluate oral products (e.g., tenofovir or other non-nucleoside reverse transcriptase inhibitors [NNRTIs]) among this population if issues of potential product compliance and follow-up are sufficiently or creatively addressed.

Outside of the IDU population, the HIV incidence is probably not sufficiently high at present for an effectiveness study in preventing HIV to be feasible, although, as indicated above, this situation may be rapidly changing. In contrast, both the high prevalence and incidence of non–HIV STIs (e.g., gonorrhea, chlamydia, HPV, and herpes) among various clinic populations do provide opportunities for studies of new drug products or for behavioral interventions (see key question 9 below) which could also be implemented in the high-risk populations. Despite this, no single center will probably have sufficient numbers of potential participants to conduct stand-alone clinical trials, but rather would need to participate in a multicenter trial, perhaps one that is international in scope.

The assessment team did not find examples of any centers having previously participated in Phase 1 (safety) trials of either contraceptives or STI prevention/treatment products. With appropriate training, however, it may be feasible for several of the sites visited to conduct Phase 1 safety trials of vaginal products, given the extensive experience of some of the centers with colposcopy. In the next year, supporting the development of GCP Phase 1 capabilities for studying microbicides within one or more institutes would potentially benefit Russia, as new products are developed in Russian laboratories and become ready for early clinical testing done to international standards.

Training for Phase 1 microbicide trials could be done in conjunction with a small study of the locally produced and marketed product, Myramistin (a product purported to have both protective and curative properties against a variety of pathogens).

In the next two to five years, Phase 2/3 trials of microbicides for protection against non-HIV STIs could be supported. HPV is a highly prevalent infection, and there would be many opportunities to evaluate vaccine approaches collaboratively with industry. Depending on the safety findings for Myramistin, effectiveness trials done to international GCP standards could be supported and involve a number of Russian clinical centers. The Ott Institute of Obstetrics and Gynecology has developed a product effective against herpes, which could also be evaluated in clinical trials.

We were told by Dr. Karamov of the Ivanovsky Institute of Virology that the state currently supports only two programs related to microbicides: One is a collaboration between St. Mary's Hospital in London and the Russian AIDS Center, and the second is an International Science and Technology Center (ISTC) project in collaboration with VECTOR (with Biotechnology Engagement Program [BTEP] funding). Russian scientists could benefit, as have United States scientists, from increased state support for microbicide research and development. There needs to be changes in policies to facilitate development and testing of microbicides, in particular against HIV, in Russia.

Challenges for conducting clinical trials. Many of the organizations and institutes with whom we met described the current state of flux of Russian regulations for clinical trials. This issue is more fully discussed in key question 5.

Other issues noted:

- *The need for a specific license from the government to conduct clinical trials.* While there may be only a few obstetrics/gynecology groups licensed to conduct these trials, a quick search of the web uncovered what appears to be dozens of ongoing clinical trials being supported by multinational pharmaceutical companies and facilitated by CROs. Licensure, therefore, while the process is unclear to us, may not be that difficult to obtain. An action item might be for the Mission to support someone to clarify the requirements and process for trial site licensure.

- *Health insurance coverage for doctors and participants.* While health care is generally free in Russia, free services require one to be in their place of registration. Outside this home location, access to services requires paying for services or purchasing additional health insurance coverage, which is generally expensive. In addition, services for sexually transmitted diseases are generally not covered by these insurance policies. The Mission could consider discussions with insurance companies to encourage change in this discriminatory practice.

- *The current system for providing treatment and care for STIs, in particular HIV/AIDS.* HIV prevention trials mandate local, easily accessible care and treatment for individuals who seroconvert within a clinical trial. However,

referrals for care of HIV positive individuals can only be to their place of registration, which could be a substantial distance away.

Some additional challenges for conducting clinical trials in Russia, in particular for investigator-initiated research, include the items that follow.

- Limited knowledge of English among health care professionals and clinical researchers poses challenges to international collaborations.

  - Using any of the clinical institutes as a site in a multinational trial will be complicated due to limited knowledge of English (all essential study documents including protocol, study manual, data collection forms, and informed consent should be translated into Russian; training can be done only through an interpreter, etc.).
  - Limited knowledge of English makes attending international conferences and seminars less valuable; it also complicates dissemination of results through submissions to international journals. Although this constraint is applicable to all researchers, it is particularly problematic for clinical researchers.

- No continuing education and training in reproductive health limits exposure to and acquisition of up-to-date knowledge.

- There is no easily available access to current scientific literature.

- There is insufficient knowledge of the basics of clinical research among clinicians involved in clinical trials, which requires more intensive training prior to and during studies.

- The insufficient experience of local ethical committees and limited education in research ethics among research staff involved in clinical trials is a challenge.

- The absence of adequate biostatistical and data management infrastructure makes it impossible to develop independent clinical research protocols that would meet international standards and requirements. Relying on just the available local staff competencies is inadequate for the needs of such studies absent skill development projects.

<u>Key Question 5.</u> *What is the regulatory environment for clinical trials as well as other stages of research and development for reproductive health technologies in Russia? For example, what are a) the administrative requirements for approval, conduct, and oversight of research (including local ethical and scientific review, central review, requirements for import of products for clinical research, etc.), b) the extent of ethics and Good Clinical Practice training at various locations, c) the ability to perform research of adequate quality to use for product registration, d) the restrictions on export of preclinical and clinical specimens and/or data for use by collaborating parties? Are there constraints on intellectual property rights that potential collaborators need to be aware of?*

Consistently applied, stable regulations for nonclinical and clinical testing of drug candidates and for obtaining drug approval are essential to attract both national and international efforts in new drug development. The universal perception among the individuals we spoke with whom either wanted to participate in clinical trials or in drug candidate development projects was that regulations stemming from the adoption of the Law of Medicines of 1998 were in a state of flux at the Ministry of Health (MOH). The individuals we spoke with gave this uncertainty as one reason why they were hesitant to become involved in projects leading to drug registration. Consistent, stable regulations for drug development and registration are a sine qua non for efficient and effective activities in this area. The MOH has a web site (in Russian) devoted to regulatory issues at www.regmud.ru. The Pharminform Company presents regulatory information in English at www.pharminform.ru which provides useful, but not complete, information about the drug registration process. These sites may be accessed for current administrative requirements for approval, conduct and oversight of research and clinical trials in Russia. Requirements for drug registration are presented in appendix F. Notwithstanding the published existing federal regulations, personnel at several institutes described the various Russian regulations covering research and development of medical products and pharmaceuticals as insufficient and unclear.

The assessment team learned that under current regulations, United States FDA–approved drug registrations are not automatically accepted in Russia and that the MOH may require additional in-country clinical evaluation to support registration.

Even within this yet-to-be stabilized regulatory environment, international pharmaceutical companies do successfully register new drugs in Russia. Assistance in dealing with regulatory procedures and product registrations is available through contract research organizations (e.g., PARAXEL International, Evidence, PSI Pharma Support, PPD Inc., Quintiles). The multinational pharmaceutical companies who conduct research in Russia appear to depend on these organizations to help navigate the Russian regulatory process to get clinical trials approved. CRO services are available, at a price, to the institutions with whom we met.

Support for in-country presentations by international CROs and professional organizations should be provided for instruction in good clinical practices and in the conduct and management of drug development programs.

Regulations per se are seldom adequate in the absence of guidelines for compliance with the regulations. Guidelines providing acceptable means of meeting the regulations remove ambiguity and greatly increase the efficiency of the drug development process.

As an advocacy project, assistance to expedite stabilization of regulations emanating from the Law of Medicines of 1998 through collaboration with United States and European drug agencies would be helpful. This exercise should extend to the issuance of a comprehensive series of guidelines to facilitate compliance with the regulations. Significant value would derive from coordinating the input of relevant international organizations (e.g., U.S. FDA and European Union–International Conference on Harmonization [EU–ICH]) to facilitate the efforts of the MOH to produce a set of guidelines which investigators/companies could follow in order to implement studies in

accordance with regulations. Relevant topics for the guidelines can be obtained at: http://www.fda.gov/cder/guidance/index.htm.

Although the ability to conduct quality clinical trials is apparent, it is not evident that all the skills exist to design and implement studies in accordance with generally accepted quality assurance procedures so that the results will be considered meaningful by the international community. For those studies which are not conducted as a member of a consortium, it is imperative that biostatistical analysis, data management and project management capabilities be available to the institutions interested in the design and implementation of their stand-alone studies.

Quality of research output is critical to the international acceptance of scientific/medical ideas, drug candidates, and manufactured drug products. Institutions that want to participate in international health programs need to adopt the *philosophy* as well as the procedures of GCP, good laboratory practice (GLP), and good manufacturing practice (GMP) along with rigorous data management and biostatistical functions. Financial and technical assistance is available (through eliciting bilateral help from United States and European standards bureaus, such as FDA, EU–ICH, and International Organization for Standardization (ISO) functions, and from quality control/assurance organizations, such as the Regulatory Affairs Professionals Society [RAPS]). The assessment team was told that the Russian MOH is about to sign a memorandum of understanding with FDA regarding GLP standards. They will attempt to harmonize preclinical testing requirements between FDA and Russia, possibly along the lines of the ICH content.

There were no reported restrictions on the export of preclinical and clinical specimens other than good handling practices for potentially hazardous materials. Nor were constraints on the exchange of data noted.

It was mentioned that the value added tax (VAT) was applied to drugs used in clinical trials, and was perceived as adding an unnecessary expense to the cost of conducting a clinical trial.

The protection of intellectual property in Russia is dubious at best. Although a patent system is in effect, it is commonly reported that international patents are violated and that confidential proprietary information and contractual terms are frequently abridged. Knowing that the security of ideas, compounds, processes, and regulatory applications is vulnerable requires international collaborators to implement appropriate procedures for their own protection. Bringing respect and protection of property and contractual rights into conformance with generally accepted international business practices would enhance the probability that Russian organizations can participate in the early development of cutting-edge technologies offered by international collaborators, especially those from the for-profit sector. The pharmaceutical industry is particularly sensitive to issues of copying patented drugs and to distribution of licensed products into secondary markets.

> Key Question 6. *Are there specific technologies or technical programs in Russia that are linked to commercial channels and capacity that could not only advance research on new contraceptives, microbicides, or other reproductive health technologies, but promote future manufacturing and/or distribution (inside or outside of Russia) of such products as well?*

The assessment team found that the linkage between biomedical research and commercial development in Russia is not robust and could benefit from additional resources. However, the assessment team did find some efforts to link technology to commercial channels. Every research institute the assessment team visited has some links to commercial channels. Institutes varied widely in their pursuit of commercial ties, from some that wait for companies to contact them, to others that already sell their own products, to those looking to go beyond their own marketing to pursuing their own production capability. In addition, the team met with associations that represent groups of research institutes. These associations help their member institutes link to commercial channels by publicizing promising research leads, identifying potential commercial partners, and providing training in business planning, marketing, and technical subjects, such as GLP. The commercial channels above include specific technologies and technical programs that can advance research on new contraceptives, microbicides, and other reproductive health technologies (please see appendix C).

These commercialization channels could benefit from support in a variety of areas, notably Center of Modern Medical Technology (TEMPO)-style training and marketing support. Technologies that are part of the above commercial channels include STI vaccines, STI therapies, and novel delivery systems for STI therapies. Expanding the existing scope or implementing a program similar to TEMPO for investigators in the reproductive, HIV/AIDS, and tuberculosis research areas in order that they might hone grant application, product management, and business development skills (through the use of workshops, training programs, real-world presentations and competitions) would be an efficient and effective way to address entrepreneurial aspects of drug development.

The need for technical training to support commercialization is great. While findings from fundamental scientific studies may be accepted among the international community, clinical studies, biostatistics, data analysis, nonclinical toxicology studies, pilot plant and production facilities must be in compliance with internationally accepted quality standards, be they European Commission (EC) harmonization guides, GCP, GLP, GMP, ISO, or World Health Organization (WHO) certification, in order for Russian institutions to be able to participate in international drug development and drug production activities. Ensuring that appropriate infrastructure, attitudes, and training exist, as well as appropriately updated facilities, would warrant early attention in any research and development improvement program.

Workshops on these topics would raise awareness and provide direction among investigators. CROs with in-country representation and the Drug Information Association (DIA) are resources. Institutionalizing a Russian certification program for identifying qualified individuals/laboratories/clinics would be useful.

There are specific technologies and technical programs in Russia that can advance research on new contraceptives, microbicides and other reproductive health technologies (please see appendix C). Several of the institutes are involved in collaborative efforts with international pharmaceutical companies (e.g., Schering AG, Pfizer) and health research programs (e.g., National Institutes of Health, WHO). Ensuring laboratories and clinics are in compliance with international quality guidelines (i.e., GLP, GCP, GMP) is a

fundamental requirement for advancing research in these areas and in promoting future manufacturing and distribution of such products domestically and internationally.

Support could be provided to the Microbiology Laboratory at the Ott Institute of Obstetrics and Gynecology to conduct a validation study of the locally manufactured polymerase chain reaction (PCR) assay kits (Lytech, Moscow, Russia) versus internationally approved kits. If the Russian kits prove to be accurate, the purchase by USAID and use of these assays may be recommended for the HIV programs in Russia and in developing countries.

> Key Question 7. *Are there particular existing institutions or private sector commercial entities in Russia that could be considered as potential and advantageous partners for manufacturing of new contraceptives, microbicides, or other reproductive health technologies, including their formulation, delivery systems, packaging, or related materials, etc., especially for provision of such products through public sector programs in developing country and low resource settings?*

There is likely to be little if any manufacturing capacity in Russia that can currently produce microbicides or other reproductive health technologies to United States GMP standards. However, reproductive health technology production is an area of potential in Russia, and we were able to identify several potential partners.

Russia's overall pharmaceutical manufacturing capacity is not enough to meet its domestic consumption. In part, this is a legacy of the Soviet period, when drugs were mostly produced in other Soviet republics or in Eastern Europe. In reproductive health technologies, market size may exacerbate the overall shortcoming of domestic production. With a population of 146 million, the economics of providing contraceptives and microbicides solely for domestic consumption is problematic, particularly for the latter, where the growing incidence of HIV/AIDS is perceived to result principally from practices of intravenous drug users, not with intercourse. There is, however, growing evidence about HIV/AIDS bridging to the general population from IDUs. USAID estimates that about 860,000 HIV–positive people currently live in Russia. Other independent agencies estimated that as much as 1 percent of the Russian population is HIV–positive. Many of the HIV/AIDS cases are among people 18 to 29 years old, and more than 40 percent of the HIV cases reported in this year are among young women infected through sexual contact (Kaiser Network, March 16, 2005).

While the assessment team did not visit any manufacturing sites, we understand there are several current or planned production facilities that may be able to support USAID health programs in Russia. The vaccine facilities, of potential interest for production of contemplated contraceptives or anti–HIV agents, are predominately inactive or have underutilized capacity

Independent of the Russian market, export of products to Eastern European, Africa and Asia is economically attractive and would be facilitated by manufacturing products, which in many instances would be under licenses from the innovator company, under conditions which meet generally accepted GMPs.

This would take advantage of a movement in Russian pharmaceutical manufacturing towards internationally accepted GMPs. The MOH mandated compliance with international GMP standards by January 1, 2005. Exactly how many Russian manufacturers successfully met this mandate is unclear, but it is clear that many Russian producers have achieved or are moving quickly to achieve compliance. Several of these producers are potentially advantageous partners for USAID. Among the organizations visited by the assessment team, one company, InfaMed, is in the process of constructing a new, international GMP–compliant facility to produce and package its surfactant product with claims of contraceptive and microbicidal activity. Two institutes, the State Research Institute of Highly Pure Biopreparations and the Research Center for Molecular Diagnostics and Therapy, are constructing GMP–compliant facilities for vaccines and other medical preparations, and have expressed some interest in potentially producing reproductive health technologies, given sufficient incentive.

Beyond the institutes visited by the assessment team, several of the largest manufacturers in Russia already have international GMP–compliant production. Nizhpharm, Akrikhin, and Veropharm all have WHO–recognized GMP production facilities and between them produce tablets, capsules, and ointments for a wide range of applications, including antibiotics, antivirals, and oncology drugs. We did not assess their costs of production or interest in reproductive health technologies, but they represent a group of proven quality producers who may be appropriate partners.

There are also several associations that could help identify further production capacity that could be part of USAID health programs in Russia. The Association of Russian Pharmaceutical Manufacturers (including Nizhpharm, Akrikhin, and Veropharm) is an industry group that advocates improvements in the quality of Russian manufacturing to improve opportunities for both domestic and export marketing. Other groups such as Pharmask, Immunogen, and TEMPO should also be able to provide information on possible manufacturing linkages.

> Key Question 8. *Are there opportunities to collaborate on early stage technology research and preclinical product development that would advance reproductive health interests in Russia?*

The assessment team was able to discuss past and current work, interests, and ideas for potential future collaborations with investigators conducting early stage technology research from the following institutions:

- Ivanovsky Institute of Virology (Russian Academy of Sciences), Moscow
- Research Institute of Immunology, Moscow
- Institute of Protein Research (Russian Academy of Sciences), Puschino
- Shemyakin & Ovchinnikov Institute of Bioorganic Chemistry (Russian Academy of Sciences), Puschino
- Institute of Physiology and Biochemistry of Microorganisms (Russian Academy of Sciences), Puschino
- Center for Toxicology and Hygienic Regulation of Biopreparations (seen at Puschino)
- Research Center for Molecular Diagnostics and Therapy, Moscow
- Institute of Physical-Chemical Medicine, Moscow
- G. Gauze State Institute for New Antibiotics, Moscow

- Pavlov State Medical University, St. Petersburg
- Research Institute of Highly Pure Biopreparations, St. Petersburg
- Institute of Cytology (Russian Academy of Sciences), St. Petersburg

The disciplines identified in the institutes listed above indicate the wide range of expertise available from the many researchers that the assessment team met. Information regarding the individual investigators, their particular expertise and interests, the nature of their institutes and funding, and other notes relevant to their individual participation in future collaborations are included as part of appendix C. Not every research program or interest of these investigators was strategically linked to the development of a health technology product, but many were, or had, significant potential applications or implications for product research and development. With these details presented in appendix C, the key question 8, regarding potential opportunities to collaborate on early stage health technology research, is addressed more broadly in the response below.

Uniformly, all of the scientists engaged in early stage research indicated that the last 10 or more years have been extremely difficult for research institutions in Russia. All of the institutes have been restructured, generally with severely reduced staff, and many have had to close. The institutes visited were all supported largely by government funds under the Soviet Union with money for research as well as for facilities and salaries. Under the Russian Federation, the government funds have largely been restricted to modest maintenance of the facilities and very modest salaries, with little or no support for actual research activities.

As cited repeatedly by the scientists visited, this has resulted in extremely low morale at these institutes and many scientists have left Russia for research and career opportunities abroad. Positions at private companies and academic centers in the United States were often mentioned as destinations for the staff and graduating students who had left Russia. Among the investigators remaining at the institutes, some have been unsuccessful in obtaining alternative support and they appear to be largely unable to conduct much research at all. In some cases, the loss of colleagues or historical collaborators and the approach of retirement appear to significantly reduce the motivation for pursuing new funding opportunities.

Among the institutes where the investigators are most able to maintain at least modest early stage research activities are those that have developed some profitable enterprise that allows the institute to earn money that is then used to fund research at that institute. Examples of these profitable enterprises include marketed test kits or reagents to diagnose viral and bacterial infections in animals and humans, other research reagents and equipment, and clinical services, e.g., related to blood analysis, hormone assays, and other diagnostic testing. These small enterprises appeared to be real lifelines and engines of productivity in many cases, and for some it appeared that expanding activities and increasing returns would be possible. Very importantly, some of these profits were also available to augment the very modest salaries provided by state funds, thereby making it possible for these institutes to retain staff members who are motivated to remain and contribute to research. The demands of conducting a commercial business seemed to be new and not entirely welcome for some of these scientists and they are still learning the details and skills. The geographic ranges of these efforts were the immediate urban area in some cases or the CIS region in others. It was not apparent that any products were

being marketed or shipped outside of the CIS. Although some of the institutes have Russian and other patents for their technologies, it was also not apparent that any technologies at the institutes visited had been licensed to private sector partners for manufacturing and marketing, etc., with royalties or other revenues returning to the institutes. Additional coordination or support from USAID or other donors for commercialization activities and training in small business management could be very productive for these research institutes that are now functioning as entrepreneurs. The existing TEMPO program and the new International Biotech Business Development Center located in Puschino could both be supported by the Bio-Industry Initiative (BII), which could be instrumental in this regard, at least for those institutes that qualify per the BII criteria (see below).

Some individual scientists and laboratories have also been quite successful in establishing international collaborations that provide some research support, taking advantage of existing funding programs in Russia supported by the U.S. Government and other donors (e.g., for nonproliferation), and acquiring funds for travel and meetings from professional associations and meeting sponsors. In many cases these opportunities were clearly established by the individual initiative of accomplished scientists assertively networking with their professional colleagues abroad and making very productive use of any support obtained for travel and meetings, exchange programs, and visiting professorships, in particular, to create research collaborations and attract new funding sources. Asking conference organizers for travel support had often been successful. It was repeatedly indicated by these scientists that the opportunity to participate in internationally attended professional meetings in Russia and abroad was of key importance in establishing new collaborations.

Among the existing programs (available to either some or all Russian scientists), in addition to USAID programs that were cited as being very instrumental in supporting health-related and other research in Russia, are the following, most of which were mentioned repeatedly. Some sponsors are indicated in parentheses and more information about these programs is included in the response to key question 13.

- International Science and Technology Center (ISTC), United States and other nations
- Biotechnology Engagement Program (BTEP), DHHS, implemented with U.S. State Department funding
- Bio-Industry Initiative (BII), U.S. State Department
- Civilian Research and Development Foundation (CRDF), U.S. Government and private funding
- Center for Ecological Research and BioResource Development, BII funded
- Center of Modern Medical Technology (TEMPO), BII funded
- Soros Foundation/Open Society Institute-Russia (not currently active in Russia)
- WHO, United Nations Children's Fund (UNICEF), and Joint United Nations Programme on HIV/AIDS (UNAIDS)
- U.S. Department of Health and Human Services, other than BTEP, including CDC, NIH, and FDA

Even relatively small amounts of money obtained through these programs were often said to be very useful because they allowed for travel to meetings, the purchase of essential equipment, or the additional salaries for needed staff.

Very practical and focused training programs were also cited as opportunities that had been instrumental to advancing the technical competence of particular laboratories and institutes. Among these were the 1 to 2–week workshops sponsored by CDC and FDA to introduce GLP, GMP, and GCP principles to the participants. International standards for animal toxicology and international guidelines for human subject protection were also identified as training topics that had been useful in the past. In some cases, such training is required for the institutional certifications or accreditations that are needed to meet international standards and to qualify for international contracts. In the past there has been some confusion regarding laboratory accreditation, for example, and the Russian attestation procedure to get an allowance to perform laboratory testing. The latter appears to be more like a license that requires a list of approved procedures and personnel, but does not have the same quality assurance requirements. Workshops on grant writing, especially for NIH proposals, were specifically asked for in response to a question from the assessment team about what kinds of training would be useful in the future.

USAID/Russia Options to Support Early Stage Health Technology Research by Russian Scientists

A variety of options for supporting early stage research in health technology and the research and development of new health products could be considered by USAID/Russia depending on their strategic fit with other initiatives, the time and effort by USAID staff that can be devoted to this purpose, and the level of available funding. A number of these options are described below.

a) With a relatively small amount of effort and funds, it would be very useful to create or adopt a list serve of Russian health science researchers that includes all relevant persons in the Russian Academy of Sciences, the Ministry of Health and Social Development, Ministry of Education and Science, and other key state agencies related to health. This list serve could then be used to periodically inform researchers of existing opportunities for support or training, e.g., through the programs and donors listed above (with information about application or registration deadlines and web sites), and to highlight the health and research priorities of USAID/Russia. Announcements, requests for activity (RFAs), and requests for proposals (RFPs), and links to relevant USAID, DHHS, WHO, UN and other agency web sites could be included. Information about USAID core-supported research programs, e.g., through the Bureau for Global Health, could be included to identify potential collaborations that could be supported through sub-agreements where possible.

b) With relatively modest and discrete additional levels of investment, USAID/Russia could consider support for other important but small-scale programs, such as travel funds to HIV or reproductive health conferences. These could be defined in terms of the number of dollars available per year, or the number of travelers to be supported, or both. A few Russian investigators were able to attend the Microbicides 2004 Conference in London in April 2004, and funds to support travel to the Microbicides

2006 Conference in Cape Town would be extremely useful if not available from other sources to help these investigators stay productively engaged in this field. The International AIDS Conferences, the annual Conference on Retroviruses and Opportunistic Infections, and the meetings of the International Society for STD Research are also valuable for investigators in early stage microbicide and other HIV research. Other areas of health and technology research have many useful international meetings as well.

c) USAID/Russia has a significant history in creating successful exchange programs for scientists and technical experts. Early stage research in targeted reproductive health areas such as microbicide and contraceptive research and development have developed a variety of specific and useful models for laboratory and animal research that are not necessarily used in an identical fashion by all investigators in the field, but which do need to be well understood by investigators who are trying to derive new data and integrate it into the field overall. Laboratory evaluations for activity against HIV, other pathogens, and fertility, as well as for cell and tissue toxicity, are examples of these models. These are also areas of research that are characterized by a great deal of fruitful collaboration and confirmation of data between laboratories. As an example, investigators at the Ivanovsky Institute of Virology in Moscow appear to have a commitment from Dr. Robin Shattock's laboratory in London to be trained in the technology of an extremely useful cervical explant model developed for microbicide research, but to date there has not been support for the travel and other associated costs involved in transferring the technology and skills to the group in Russia. Other examples could be identified and solicited from investigators in the field as well.

d) In selected cases, it may also be very instrumental for USAID/Russia to consider supporting, in part or whole, meetings, workshops, or conferences of various sizes that would allow Russian researchers to meet together, discuss the status and progress of work on specific health technologies, and get feedback from colleagues in that field from Russia and abroad. For example, a small group of Russian investigators interested in microbicide research and development met in November 2004 in St. Petersburg, and there appears to be interest in holding another meeting in 2005, if possible, with more international attendance. Although travel support for Russian investigators to attend microbicide meetings abroad is undoubtedly useful as well, microbicide research and development is a nascent field in Russia and a field to which the existing expertise of Russian investigators could contribute a great deal. Well-planned meetings in Russia that could be attended by new investigators and students could advance the field enormously, and merit support from USAID/Russia or others.

e) If a sufficient but not necessarily large amount of funding was available, a strong development and scientific rationale could be presented for supporting early stage research at a number of the institutes visited by the assessment team. As described above, it was very clear to the team that many of the researchers were quite accomplished in their fields and had the present capacity to be much more productive if they had more resources to work with. The Ivanovsky Institute of Virology serves as a good example again. The investigators that the assessment team met were clearly knowledgeable of the major leads and issues in microbicide research and

development, and had the qualifications and interest to do much more in this field. Although the experience of the assessment team was necessarily limited, there were brief discussions with investigators working on other health technologies, for example on various vaccines in particular that sounded very worthwhile and promising. If USAID/Russia had, for example, $50,000 to $100,000 to invest in advancing early stage research in a targeted area of health technology, it might not require too much additional effort to identify a worthwhile laboratory to use the funds, given the significant unused capacity now available in Russian research institutes.

f) A larger research funding program to support health research of high priority to USAID/Russia would certainly be justified if more resources were available. Although some of the other donor programs in Russia have a very broad scope of activities that can potentially be supported, USAID/Russia could very effectively target research that contributes to the USAID health and development objectives in particular by soliciting proposals in defined areas. These could be publicized in part using new or existing list serves of scientists in Russia. The commitment of staff time, administrative effort, and other resources for a larger process that includes soliciting and reviewing competitive proposals is obviously considerable.

g) The above options could largely be implemented unilaterally by USAID/Russia staff. There may, however, be some really significant opportunities to collaborate with some of the existing research support programs that are described above and that were often cited by Russian scientists as being effective and valuable. For example, for the existing training in GLP, GMP, and GCP, it might be sufficient to help publicize the existing opportunities and/or cover the cost of trainees selected by USAID/Russia, but if the capacity or entry criteria of the existing training is limiting, it might be very cost-effective for USAID/Russia to collaborate with CDC, FDA, or others to cover the costs of expanding the existing sessions or to cover the costs of additional sessions for trainees that USAID has selected. DHHS also sponsors grant writing workshops in various locations around the world. If they are not held in Russia, or if the capacity is not sufficient, USAID/Russia might be able to share or cover costs for these workshops. Russian scientists expressed an interest in these workshops and they could certainly be a good investment for all concerned.

h) A number of the scientists that the assessment team met indicated that they had benefited from the existing programs that have nonproliferation objectives. The programs mentioned included the International Science and Technology Center, the Biotechnology Engagement Program, and the Bio-Industry Initiative, in particular. Although the qualifications required for primary participants in these programs seemed to be clear, in some cases there was uncertainty about the opportunities and potential roles for collaborating investigators. It may be possible to advance the objectives of these nonproliferation programs as well as other health and development objectives of USAID/Russia by facilitating collaborations between investigators that qualify for the nonproliferation programs and investigators who do not qualify independently but could clearly contribute to the nonproliferation objectives as collaborating investigators or in some other essential role as a sub-awardee. This facilitation might be achieved primarily through communications (e.g., via list serves) to inform health science researchers more broadly about the current participants and

activities of these nonproliferation programs as well as about future opportunities to submit proposals. It was not evident that the number and qualifications of the eligible participants for the nonproliferation programs is ever subject to review or modification, but if these issues are periodically reconsidered, it may be useful for USAID to contribute to the discussion. Good communications with the sponsors and administrators of the nonproliferation programs would clearly be productive in achieving these and other shared goals, in any case.

i) As mentioned above, a number of the Russian institutes are already engaging in significant entrepreneurial activities that are extremely important in allowing them to support their research activities. Some of these efforts might be even more successful with some technical assistance in business management and commercialization of product or service leads. Although assistance of this type seems to be available through some of the existing programs from other agencies (e.g., BII, in particular), it was difficult for the assessment team to fully delineate the criteria and limits for participants in these programs and to identify where there were or were not opportunities for some of the institutes that the assessment team visited. If USAID/Russia could identify and address some of these gaps or otherwise facilitate business opportunities inside Russia or internationally for the institutes that are interested, it might be very useful in ensuring the sustainability of their research programs. This would be especially fruitful, of course, if an institute developed an important health product that could be cost-effectively marketed in developing countries or to donors for programs in developing countries.

j) Another element of business management for health technology and product research and development that is critically important for international collaborations, and was confirmed to be problematic numerous times by persons visited by the assessment team, is the limited understanding and acceptance of intellectual property rights (IPR) in Russia and the history of inconsistent and unethical practices in this regard by some Russian businesses and researchers. It was said that some companies (e.g., multinational pharmaceutical companies) that are concerned about market rights and exclusivity are reluctant to enter collaborations in Russia that put intellectual property at risk. It was reported that data are often sold or made available to other companies and that the original collaborator has no legal recourse in Russia. Presumably, these IPR issues are well addressed in some of the existing commercialization and business development programs, but this is another area in which USAID/Russia may be able to target or augment these efforts to ensure that they are effective in the context of health product research and development and that relevant programs are available beyond the nonproliferation participants. This is partly a need for training and establishing higher standards of conduct for researchers and entrepreneurs, and partly an issue of national policy and judicial reform.

k) A number of the scientists that the assessment team met also indicated that they had benefited through programs provided by the Soros Foundation (www.soros.org) and that these programs were no longer available because the Open Society Institute-Russia had ended operations as a foundation in Russia. The assessment team did not have the opportunity to research the scope and impact of such programs in depth, but the loss of these and other programs that are widely regarded as effective and appreciated in supporting health science through research funds, training, policy

development, or other initiatives, is unfortunate. Although programs may end for a variety of reasons, in cases where the merit of the objectives is still great, where public awareness has been created, and where an administrative mechanism has already been established, it may be very effective programmatically for USAID/Russia to promote the continuation of these or similar programs with alternative sponsors or sources of funding. This may, of course, be difficult.

l) A variety of partnerships between the public and private sectors in Russia are occurring in many fields at this time. Early stage research contributing to health science broadly, and in many cases, to health technology and product development, might be an attractive area for combining complementary assets from the public and private sectors. For both sectors, potential partners could include parties in Russia or abroad. Whether there are promising opportunities for such a partnership to be formalized as a USAID Global Development Alliance (GDA) is not completely clear to the assessment team, but it is very evident that a considerable amount of scientific expertise and personnel time in key health-related disciplines is being greatly underutilized in Russia and offers a potentially great value in many ways to both private and public sector interests. Reportedly, the process of identifying partners and defining relationships for such alliances is generally uncertain and somewhat serendipitous, but USAID has a GDA Secretariat office that provides guidance and training if that would be useful to staff at USAID/Russia. Private sector partners do not necessarily have to be major corporations or foundations with large financial resources, although they sometimes are. The assessment team heard a number of references to Eli Lilly (possibly the company or the foundation), which has established a research and training program on multidrug-resistant tuberculosis in Tomsk, Russia, in partnership with Harvard University. This may, in part, be a model for potential USAID alliances. Moreover, in some cases, the inclusion of the United States or other major academic center outside of Russia as a partner may be an excellent way to strengthen the potential for future international collaborations for the Russian research partner, augment adherence with international standards where applicable, and provide an effective administrative mechanism. Alliances that are either small or large, in terms of programmatic scope and financial commitments, should be considered if possible.

m) Leveraging a higher level of commitment and funds from the Russian government to support early stage research contributing to health science would also be extremely beneficial in terms of getting the most public health and development value from the existing underutilized research capacity in the Russian institutes. Although programs like the Global Development Alliances and other public-private partnerships often appear to be founded on the initiative of major public sector donors like USAID that establish relationships with large private sector partners, other combinations of partners with agreements to coordinate or match funds might be possible. For targeted activities like product development for HIV prevention and family planning, for example, it might be feasible to create a program that is co-funded by USAID/Russia in collaboration with the Russian Academy of Sciences or some other administrative body with funding authority. From very brief comments that the assessment team heard, it appears that the Ministry of Education and Science may have some interest and new grant programs starting that would be fruitful opportunities for collaborating to promote health-related research. Such

collaborations might be established as a formal agreement with matching funds, jointly solicited and reviewed proposals between both United States and Russian researchers, or alternatively as less detailed memoranda of understanding, to commit and coordinate funds for the targeted activities. Theoretically, any number of partners could participate, but the leveraging of new funds and commitment from the Russian government entities might be more difficult with a larger number of partners involved.

n) Coordination and leveraging of funds with other non–United States and non–Russian international development agencies may also have some potential, particularly in certain program areas. The assessment team was not able to collect a lot of information on the programs and interests of other development agencies, but the Canadian, Swedish, and British governments, among others, have all recently committed major new funds to microbicide development activities, for example. A more thorough review of these and other health-related initiatives from other agencies might help identify opportunities for coordination and synergy. Even brief mutual communications about the status and objectives of programs could be very useful in setting priorities and maximizing benefits.

o) The assessment team did not have substantial expertise on policy issues at this level, but it appears, for example, that support from the Russian government for education in technical and scientific fields is still sufficient for students to progress through the equivalent of undergraduate and graduate studies, but then there are none or few of the career opportunities that historically have been provided by the Russian science institutes. Although the magnitude of this problem was not quantified, it was mentioned frequently as a reason for young scientists emigrating, making it difficult for the institutes to survive, much less thrive, in research, and perhaps complicating the achievement of nonproliferation objectives as well. It was not clear to the assessment team if this situation in part reflects inconsistencies in policy between the Ministry of Education and Science versus the Ministry of Health and Social Development or other policy issues, but opportunities for USAID/Russia to advance policy changes that would increase support for early stage research at the Russian science institutes or otherwise optimize the relationship between relevant Russian government policies could be very worthwhile.

Key Question 9. *What behavioral and social science research, including acceptability of products and services, could be advanced by collaborative efforts and contribute to developing new technology, strengthening service delivery programs, and improved reproductive health?*

Contraception. Understanding the behaviors and attitudes that influence contraceptive practices is critical to understanding how to increase effective contraceptive use in Russia, and thereby reduce abortion. Modern reversible contraceptive use is low, and permanent methods are virtually absent. There would seem to be numerous potential opportunities through collaborative behavioral and social science research efforts to expand knowledge of barriers to method use, and define cost-effective programmatic options to optimize the overall method mix in Russia. Acceptability and introduction studies of contraceptives can be done at a range of sites and on a number of

programmatic levels; they are not, however, currently identified as a focus of activities for any of the health professionals visited by the assessment team.

Voluntary sterilization, both male and female, is very limited across Russia. Indeed, vasectomy may be essentially unavailable. The reasons are unclear. There may be provider as well as user barriers. Surgical female sterilization and vasectomy constitute a substantial percentage of the method mix in many developed countries, and provide safe and effective contraceptive options for individuals who have completed their families. Increased use of sterilization could readily contribute to reducing abortion rates in Russia. Several behavioral research opportunities should be considered to improve understanding of the barriers to contraceptive services, and ways in which these barriers could be reduced and demand increased.

- Review the training program sponsored by EngenderHealth several years ago to determine the issues and reasons that expanded use of female sterilization never "took off."

- Conduct surveys and/or focus groups with providers and with users to explore perceptions of female sterilization and vasectomy.

- Conduct formative research in a limited number of high-volume family planning clinics with the potential to offer female sterilization (or vasectomy) to determine what messages might help to improve acceptability and uptake.

- Conduct a small introductory program offering female sterilization, and follow users to evaluate satisfaction.

- Conduct a pilot activity offering female sterilization in a postabortion care setting (perhaps to women who have had multiple abortions and are older). and evaluate acceptability among users.

- Conduct formative research among urology centers to determine the receptivity to vasectomy (the assessment team did not visit these centers, so cannot speak directly to the potential of this proposal).

- Conduct a pilot program to offer vasectomy and conduct qualitative surveys to determine acceptability and satisfaction.

HIV and potential microbicide issues. Understanding behaviors that put people at risk of acquiring HIV remains one of the fundamental challenges of HIV/AIDS prevention. The epidemic in Russia is beginning to change, expanding from predominantly an intravenous drug user population into the general population. If the epidemic quickly moves, as it has in other countries, information will be rapidly needed to help programs identify individuals at risk, provide testing and counseling, and appropriately target both prevention and care programs. Indeed, there is a suggestion of this rapid bridging to the general population, in that some 40 percent of new infections in 2004 were reported to be among women through heterosexual contact (Kaiser Report, March 2005).

Several behavioral research opportunities should be considered, with immediate opportunities for adding further behavioral research to the existing Russian Association for Prevention of Sexually Transmitted Diseases program. They are:

- Explore acceptability and use of female condoms among high-risk populations, given the high incidence of STI. Immediate funding could be provided to SANAM for this research.

- Funding could be provided to allow SANAM to expand their activities and increase the number of high-risk target groups for outreach work, including some of the bridge populations of great importance to stemming the HIV epidemic.

- Behavioral research could address the contexts and determinants of behaviors associated with the transmission of HIV in potential bridging populations, and rapidly evaluate methods for modifying behaviors and focus on prevention.

- Behavioral research could provide valuable insights into the potential for microbicide introduction in Russia.

Key Question 10. *What efforts are needed and possible to build research capacity in any area contributing to improved reproductive health in Russia?*

Russia contributed significant fundamental science and medical findings in the past through its internationally renowned scientists, clinicians, and laboratories. Their capabilities were severely compromised following 1990 when the Russian federal government reduced financial support to university and academy scientific and medical programs. With little more than marginal salaries and support for building maintenance and utilities available from government budgets, the assessment team found funding for adequate salaries, supplies, equipment, clinical trials, upgrading of processes and procedures, collaborations, and international travel ranged from limited to nonexistent—a situation sorely in need of correction through increased funding, technical assistance, and collaborations. While not all of the existing federally supported scientific infrastructure can be supported, there are many organizations conducting fundamental and preclinical research worthy of increased attention from the Russian government.

The clinical institutions visited by the assessment team (please see appendix B) have many highly trained and skilled individuals with experience in providing clinical care across all areas of reproductive health. Few of these individuals have been involved in clinical research. Fewer have actually prepared their own protocols and been involved in the analysis of trials that would meet international standards. It appears that the substantial majority of contraceptive clinical trials conducted over the last five years have been done in collaboration with multinational pharmaceutical companies (who designed and analyzed them). Therefore, the concepts of clinical trial design and the challenges of developing protocols that meet rigorous statistical requirements are foreign to most clinicians and researchers. Training encompassing the breadth of activities relevant to designing, implementing, and analyzing clinical trials would be important to fostering the future ability of Russian centers of excellence to lead research of potential new Russian reproductive health products. Such design and implementation training is also essential

for international acceptance of future clinical research results.

Clinical research capacity. The optimal means for building research capacity is through training that is followed by immediate and direct implementation experience. Stand-alone training, while of interest to sites, generally will not have a long-term impact, and the knowledge gained will quickly fade if not used. Also, during the trial phase, ongoing monitoring and technical assistance is ideal. The organizations we visited all state that they understand the philosophy and rigorous standards attached to GCP compliance. They indicated that a proportion of their staff has had some type of GCP training. However, the nature of this training and its duration was not clear, and few of the staff subsequently put the concepts to use. In addition, training on research ethics for both researchers and institutional review boards has been lacking. Biostatistical training specific to the design and analysis of contraceptive trials would also be important for institutions involved in developing their own research studies in this therapeutic area.

Recommendations that could immediately improve clinical research readiness:

- Translate FHI's Research Ethics Curriculum that is used by many international organizations for training into Russian, with subsequent training on and dissemination of the document. The curriculum is currently translated into five languages and has been successfully field tested and implemented in practice in many countries.

- Workshops and training for local ethical committees and exchange of experience among these committees.

- General workshops on clinical trial design, methodology, main principals of biostatistics and data management, international terminology and classifications. Development and translation into Russian of a corresponding manual for clinicians involved in clinical research.

- Short-term training on principles of GCP.

- Short-term training for staff involved in developing protocols for new Russian product clinical trials. For example, when a new product is about to enter clinical trials and sites are assigned by the MOH for conducting these trials, provide technical assistance in study design to the local principal investigator and key study staff. Alternatively, provide short (2 to 4–week) trips to host institutions (FHI, WHO, CONRAD, others) to develop protocols.

- Data management and biostatistical training, perhaps through establishing a collaborative relationship with an international organization using the model of the International Clinical Studies Support Center (ICSSC, http://icssc.org/index.htm), an NIH–funded network coordinated through FHI.

Behavioral research capacity. Behavioral research is greatly needed to expand modern contraceptive use and perhaps more importantly, to help prevent the potential explosion of HIV into the general population in Russia. As with clinical research, the optimal means for building research capacity is through training that is followed by immediate

and direct implementation experience. Our team predominantly met with clinical service providers and researchers, and with the exception of staff at SANAM, did not meet with individuals conducting behavioral research or behavior change interventions. Therefore, we have a limited ability to comment on overall capacity for behavioral research in Russia. Still, the recommendations below could be broadly implemented to increase capacity, as the issues facing Russia, in particular with regard to the growing HIV epidemic, are enormous. It would seem that behavioral research focusing on populations not previously deemed to be at risk will be important in the near term.

Recommendations that could immediately improve behavioral research capacity:

- General workshops on qualitative and quantitative behavioral research design, methodology, and main principals of biostatistics and data management as related to HIV–prevention research.

- Short-term training for staff interested in designing and implementing research to define strategies for risk-reduction related to STIs, or for understanding, designing, and implementing research to expand use of effective contraceptive methods.

- Workshops for Russian researchers interested in expanding behavioral research on HIV prevention, during which proposals are developed for submission to a small grants program.

- Develop a small grant program that funds behavioral research projects and expand behavioral research capacity in important, strategic areas for USAID and the Russian government.

In addition to the above more specific recommendations, the following general recommendations could enhance capacity and facilitate research:

- Improved access to modern literature through Web-based programs (e.g., Pubmed, MedLine), through individual journals specialized in the area of STIs and contraception, and subscriptions to Cochrane Library of evidenced-based medicine.

- Refresher training in reproductive health (family planning, HIV treatment and prevention, STI).

- Training courses in English for clinical researchers.

- Support for microbicide research in Russia could potentially be expanded through greater advocacy and visibility. To this end, the United States-based Alliance for Microbicide Development might be able to provide insight and guidance on the processes they have pursued to expand financial support to United States organizations.

Key Question 11. *What is the current and future potential to use capacity and expertise already existing in Russia to provide technical assistance, training,*

service delivery, and other contributions to advance reproductive health services and research programs in developing countries, e.g., in Africa?

There is a current potential to provide technical assistance to advance reproductive health programs in developing countries, especially given the previous experience of the Soviet Union in providing such assistance. The assessment team met with a number of highly skilled, knowledgeable physicians who could be involved in providing technical assistance and training in developing country program settings. However, a broad training effort should be undertaken in order to provide up-to-date information, including modern terminology, classifications, approved standards and internationally recognized recommendations (e.g., WHO, IPPF, CDC), for Russians who are engaged in technical assistance assignments. Limited knowledge of English or other language, e.g., French, in which training is often conducted, can be a potential obstacle. Additional training in English (for English-speaking African countries) may be considered.

The Ott Institute in St. Petersburg is in involved in a Russian-Swedish project "Improvement of the prevention and control of sexually transmitted infections in Leningradskaya Oblast." This program is supported by the health committee of the Leningradskaya Oblast and aims to improve the quality of the management of STIs in this region. This fascinating project draws in key individuals in obstetrics, gynecology, urology, and dermatovenerology within the oblast. This collaborative project could be replicated in specific developing countries. Individuals who are involved in these activities would be good resources to include in transferring clinical experiences to other settings such as Africa.

Key Question 12. *Are there other ways, not included above, that USAID could use the scientific community in Russia to advocate, support, and advance reproductive health research programs?*

The assessment team feels all reasonable suggestions are expressed in responses to the other key questions.

Key Question 13. *What types of financial and other investments would be needed to pursue any opportunities in the above areas, and by whom?*

Among the existing programs (available to either some or all Russian scientists) cited as being very instrumental in supporting health-related and other research in Russia are the following, most of which were mentioned repeatedly.

International Science and Technology Center (ISTC), a nonproliferation program supported by the United States and other countries to link fundamental research in Russia to commercialization and international markets, and thereby promotes the integration of Russian researchers into the international scientific community. This program focuses on opportunities for scientists whose former work was related to warfare technology.

Biotechnology Engagement Program (BTEP), developed by the Department of Health and Human Services (DHHS) with funds from the State Department to engage former biological weapons scientists in Russia in public health research.

Bio-Industry Initiative (BII), funded by the U.S. State Department to engage former weapons scientists in Russia with drug and vaccine development and to convert production facilities for biological weapons to other purposes.

Civilian Research and Development Foundation (CRDF), a nongovernmental organization (NGO) with funding from several U.S. Government agencies and private sources to support collaborations between scientists in the United States and Eurasia through grants, training, and other technical resources.

The Center for Ecological Research and BioResource Development is a new center at Puschino with 15 staff members, which started in January 2005 with a BII grant to promote entrepreneurial endeavors including research, innovation, and commercialization, and is coordinated with a new master's degree program.

The Center of Modern Medical Technology (TEMPO) is a two-year-old nongovernmental and noncommercial organization funded by BII with 11 Russian research institutes (those which were formerly part of Biopreparat, the Soviet bioweapons research organization) as members collaborating to produce vaccines and other medical products at 14 manufacturing facilities. TEMPO coordinates training programs for manufacturing and professional development and periodically reviews business development proposals from scientist inventers at member institutes.

Soros Foundation. Although the Open Society Institute-Russia is not presently operating as a foundation in Russia, a number of independent nonprofit organizations have been created and funded to continue work in key areas including education, development of democracy, cultural policy, and judicial reform.

WHO, UNICEF, and UNAIDS. The multilateral health programs funded by WHO and the United Nations that support health research and services worldwide and in Russia with an emphasis on maternal and child health, childhood immunizations, and HIV prevention.

U.S. Department of Health and Human Services (including CDC, NIH, and FDA, in addition to BTEP above). A portfolio of activities that includes research on HIV vaccines, prevention of mother-to-child HIV transmission, and training in good laboratory practice, good clinical practice, and good manufacturing practice.

Lists of recommendations and possible projects are elsewhere in this report with some notional consideration of required investments. USAID has several funding options available in pursuing its projects in Russia. The first is sole USAID funding. For any agency, this type of funding has the benefit of allowing complete control, but limitation in terms of the scope of project that may be supported. USAID–only funding may be best applied to small projects that are unlikely to match the interests of other major funders, for example a workshop focusing on Russian microbicide research regulation.

The second is joint funding with a private entity. USAID is likely to share interests with private companies, for example companies with reproductive health products ready for clinical trials, production companies that may be interested in expanding into reproductive health, and major NGOs, such as WHO.

The third option is joint funding with other U.S. Government agencies. Nonproliferation programs are a major source of U.S. Government funding for biological research and development in Russia. These programs, administered by several U.S. Government agencies, differ in their focuses and implementation, but all share a common goal of reducing the threat of biological weapons by engaging institutes and scientists who were part of the former Soviet bioweapons program. Some nonproliferation-engaged institutes are pursuing reproductive health research proposals, showing that there is potential for USAID/Russia to work cooperatively with nonproliferation programs.

However, the nonproliferation programs are politically sensitive, and working with them cooperatively would require a serious commitment from USAID. This commitment would include sufficient staff time to understand fully the procedures and priorities of nonproliferation programs, particularly BII and BTEP. This should be done via meetings with BII and BTEP representatives and attendance at interagency nonproliferation meetings. Regular coordination between the Moscow Mission and the Embassy's Science and Technology office would also improve coordination with nonproliferation programs.

In addition, the nonproliferation programs are already mature programs that actively and successfully identify, develop, and implement projects successfully without USAID's participation. In order to cooperate fully, USAID must be able to offer the resources to add to these successes, not draw away from them. Examples of potentially productive resources include not only project cofunding, but also the time of USAID scientists and other staff.

In addition to nonproliferation, there are a variety of other U.S. Government programs that support health research and development in Russia. Those identified by the assessment team as potentially beneficial partners for USAID are included in the attached list.

> Key Question 14. *What types of collaborations could be established in the next year and productively implemented in the next two to five years?*

The response to this key question summarizes all of the above recommendations, which may be considered by USAID/Russia for implementation.

The following recommendations are grouped according to whether they predominantly relate to issues regarding policy, clinical research on contraceptives, clinical research on microbicides, behavioral research, drug/product development, training, and infrastructure development. The number indicated at the end of each recommendation refers to the key question in which the issue is first presented and/or is more fully developed. Within each group, recommendations are presented in order of anticipated increasing expense and time commitment (since determining absolute dollar and manpower requirements for each project was not practical). The ordering reflects a resource constrained listing which could well differ from a priority ranking based on impact. Many of these recommendations can largely be implemented unilaterally by USAID/Russia staff.

While the discussions with staff at the organizations visited were invaluable in developing recommendations regarding both the general environment for research and development of potential health technologies in Russia and the potential for implementing specific projects at their organizations, a solicitation to the wider research community in Russia could produce additional candidate organizations for project implementation and program participation.

The following are recommendations for implementation.

Note: The number(s) in parentheses following each recommendation correspond to the 14 key questions in which the issue is first presented and/or is more fully developed (found above and in the scope of work).

Policy

1. Facilitate regular communication between USAID/Russia and the U.S. Embassy Science and Technology Office to improve coordination with other government-funded technology programs in Russia, including those with a nonproliferation focus. (13)

2. Leveraging a higher level of commitment and funds from the Russian government designed to support the early stage research that contributes to health science would also be extremely beneficial in terms of getting the most public health development value for the existing underutilized research capacity at the Russian institutes. A larger research funding program by USAID/Russia would certainly be justified if more resources were available. These efforts could be effectively combined with policy development and reform efforts as well. (8)

3. Addressing inefficiencies in health care systems would be an extremely broad undertaking in any country. There are, however, priorities defined by USAID/Russia for the integration of family planning programs with HIV prevention and treatment programs that are highly appropriate for support in a more focused program. Research is clearly needed to identify program options, estimate their cost and sustainability, and inform changes in policies. (1)

4. Russian scientists could benefit, as have United States scientists, from increased federal support for microbicide research and development. Support for microbicide research in Russia could potentially be expanded through efforts to provide greater advocacy and visibility. To this end, the United States-based Alliance for Microbicide Development (www.microbicide.org) could provide insight and guidance on the processes they have pursued to expand financial support for microbicide research at United States organizations. It may be fruitful to involve the alliance in the next microbicide conference in Russia, the first of which was held in St. Petersburg in November 2004. (2)

5. Support changes in the drug regulatory laws to facilitate development and clinical testing of microbicides in Russia. MOH requirements for preclinical and clinical evaluation of product candidates to achieve registration of a new microbicide are not well defined. (5)

6. Support efforts to clarify regulatory requirements for registration and labeling of over

the counter (OTC) products; the absence of which has allowed products to reach the market with false or unsubstantiated claims. (2, 4)

7. Support efforts to treat newly identified HIV/AIDS patients regardless of their city of origin, and to remove negative stigma associated with the HIV/AIDS disease. Consider discussions with insurance companies to encourage a change in the discriminatory practice of not covering STI services under supplemental insurance policies often purchased by Russians. (3, 4)

8. As a broader scale advocacy project, provide assistance to expedite stabilization, clarification, publication, and dissemination of regulations and their implementing guidelines emanating from the Law of Medicines of 1988. Enlist collaboration with United States and European drug agencies. This exercise should extend to the issuance (and to ensuring that drug development and clinical trial researchers are adequately informed about them) of a comprehensive series of guidelines to facilitate compliance with the regulations. Include clarification of the process by which clinical sites are registered to conduct clinical trials, and remove the need for MOH to assign sites for a specific clinical trial. (4, 5)

9. Support efforts to bring respect and protection of property and contractual rights into conformance with generally accepted international business practices. This is partly a need for training (understanding and acceptance of intellectual property rights) and for establishing higher standards of conduct among researchers and entrepreneurs, and partly a need for national policy and judicial reform. (5, 8)

10. Encourage the Russian government to reduce/eliminate the 18 percent value added tax levied against drugs used in clinical trials. (5)

Clinical Research on Contraceptives

11. Develop a list of obstetrics/gynecology and STI and other infectious disease clinical units within institutes or organizations in major Russian cities and determine which have licenses and which have done clinical research previously, in particular with pharmaceutical companies and to GCP standards. This would be an important resource for promoting future trials and collaborations. (2)

12. Based on the snapshot of clinical institutes we visited, there would appear to be many opportunities to conduct research on new contraceptives within Russia. New contraceptives could be tested within the format of Phase 1 and 2 trials in all the clinical institutes that we visited. In addition, all of the institutes can potentially serve as a site in a multicenter Phase 3 trial evaluating contraceptive effectiveness. Post-marketing Phase 4 or introductory trials can be conducted at all the clinical sites visited. (4)

13. Some institutes (e.g., Ott Institute, Research Center of Obstetrics and Gynecology and Perinatology, and the Moscow Regional Institute of Obstetrics and Gynecology) with both significant clinical reproductive health practice and GCP clinical trial experience are particularly well positioned and have the staff capacity to participate in GCP reproductive health trials with relatively minor external support. Several clinical

centers we visited had participated in multicenter trials of new hormonal methods, including implants, vaginal rings and a hormonal patch, and successfully enrolled patients in these studies quickly. This indicates a capacity that could be tapped for other, similar contraceptive trials. As an example, very little capacity building would be needed to add a Russian obstetrics/gynecology clinical center to one of the multicenter clinical trials (e.g., vaginal rings, female condoms) supported through the USAID network (e.g., via the Population Council, FHI, or CONRAD). (2, 3, 4)

14. With method mixes providing little to no female sterilization, consider an introductory trial to offer female sterilization to women with completed family size. (4)

15. Given the popularity of IUDs in Russia, conduct effectiveness studies of new intrauterine devices, including hormone-releasing devices. (3)

16. Other non–USAID funders (e.g, PATH, NIH) may welcome proposals for new, jointly funded studies in reproductive health research and development in Russia. (9, 10)

Clinical Research on Microbicides

17. Ensure continuous funding of the existing project with SANAM and consider an increase in funding which will allow SANAM to expand their anti–HIV and anti–STI activities, and increase the number of target groups for outreach work to high-risk populations and to train other anti–HIV sites. (9)

18. Use reduced transmission of non–HIV viral and bacterial STIs as end points in Phase 2–3 studies of microbicide drug candidates. For example, HPV is a highly prevalent infection, and there would also be many opportunities to evaluate vaccine approaches collaboratively with industry. In addition, following cure of bacterial STIs, reinfection rates were reported to be quite high among the high-risk population attending SANAM's clinic. This would make it feasible to conduct trials of microbicides with non–HIV STIs as outcomes, or to evaluate new therapeutic products for treatment of these infections. (1 ,3, 4)

19. Trials of oral agents to prevent HIV may be feasible with intravenous drug users but only if issues of compliance and follow-up for this population, which could be substantial, are adequately addressed. (4)

20. Phase I safety studies of Myramistin done to international GCP and microbicide development standards could be immediately funded, however, training of centers on Phase I microbicide safety trial standards would be needed. Depending on the safety findings of Myramistin, effectiveness trials done to international GCP standards could be supported, involving a number of Russian clinical centers. (4)

Behavioral Research

21. Acceptability and introduction studies of contraceptives can be done at a range of sites and on a number of programmatic levels; they are not, however, currently

identified as a focus of activities for any of the health professionals visited by the assessment team. (1)

22. The high-risk HIV/STI groups may need to be reached through nontraditional approaches. Surveillance and epidemiological studies may be especially informative to document and improve the effectiveness of risk reduction and behavior change programs. (3)

23. Explore acceptability and use of female condoms among high-risk populations, given the high incidence of STI. Immediate funding could be provided to SANAM which works with appropriate populations for this research. (9)

24. Consider behavioral research to improve understanding of the barriers to contraceptive services, and ways in which these barriers could be reduced, and demand for services increased, in order to continue to increase contraceptive prevalence and thereby reduce abortion rates. (9)

25. Conduct surveys and/or focus groups with providers and users to explore perceptions of female sterilization and vasectomy and possible barriers to broader use. (3,9)

26. Conduct formative research in a limited number of high-volume family planning clinics with the potential to offer female sterilization (or vasectomy) to determine what messages might help to improve acceptability and uptake of sterilization. (9)

27. Conduct a small introductory program offering female sterilization and follow users to evaluate satisfaction. (9)

28. Conduct pilot activity offering female sterilization in a postabortion care setting (perhaps to women who have had multiple abortions and are older) and evaluate acceptability among these users. (9)

29. Conduct formative research among urology centers to determine receptivity to vasectomy. (9)

30. Conduct a pilot program to offer vasectomy and conduct qualitative surveys to determine acceptability and satisfaction of the method. (9)

Drug/Product Development

31. Identify United States Government support and collaborations to augment the limited Russian federal support of preclinical and clinical research in reproductive health and microbicide development. (4)

32. There are significant opportunities to collaborate with some of the existing research support programs described above that were often cited by Russian scientists as being effective and valuable. A more thorough review of these and other health-related initiatives from other agencies might help identify further opportunities for coordination and synergy. (13)

33. With relatively modest and discrete additional levels of investment, USAID/Russia could consider supporting in part or in whole meetings, workshops, and conferences of various sizes. This would allow Russian researchers to meet together, discuss the status and progress of work on specific health technologies, and get feedback from both domestic and international colleagues in that field. Efforts could be focused on functions related to HIV/AIDS and reproductive health. (8)

34. USAID/Russia has a significant history in creating successful exchange programs for scientists and technical experts. Travel support from USAID or other sources for Russian investigators to attend international scientific meetings, and to support future research collaborations, could be very productive for their research. (1, 8)

35. Improve access to modern scientific literature through Web-based programs (e.g., Pubmed, MedLine), through individual journals specialized in the area of STIs and contraception, and provide subscriptions to Cochrane Library of evidenced-based medicine. (10)

36. Support the Microbiology Laboratory at the Ott Institute to conduct a validation study of the locally manufactured polymerase chain reaction assays (Lytech, Moscow, Russia) versus internationally approved kits. (4)

37. Expand the existing scope or implement a program similar to TEMPO for investigators in the reproductive, HIV/AIDS, STI, and tuberculosis research areas so they can hone grant application, product management, and business development skills through the use of workshops, training programs, real world presentations and competitions. (6)

38. Use the Center for Ecological Research and BioResources Development to facilitate regulatory process standardization and dissemination to train other Russians regarding the regulatory machinery within Russia. (10)

39. A strong development and scientific rationale could be presented for supporting early stage research at a number of the institutes (8). Research areas of particular interest to each of the organizations visited are presented in appendix C.

40. A variety of partnerships between the public and private sectors in Russia exists at this time. Support by USAID/Russia of alliances that are either small or large in terms of programmatic scope and financial commitments could be considered. (8)

41. Partner with other U.S. Government funders to support reproductive health proposals at facilities participating in nonproliferation programs An example of a project potentially meeting nonproliferation and reproductive health goals is an Ivanovsky Institute of Virology microbicide proposal submitted to BTEP. (13)

42. Partner with private funders. There are Russian companies that are devoting private capital to reproductive health work in Russia. USAID/Russia can increase the impact of these efforts through the joint funding of projects. (13)

43. There is specific expertise in Russia for the detection of low levels of biological contamination. This expertise could be very useful for monitoring the purity and safety of many medical products, possibly including disease-preventive and therapeutic products, or blood and other tissue products, as well as the effectiveness of procedures used for sterilization or purification. The possibility of transferring this expertise to developing country settings for applications in manufacturing, public health, or clinical care could be investigated in the future as appropriate. (1)

44. Export of medical products to Eastern Europe, Africa and Asia is economically attractive and would be facilitated by manufacturing products (which in many instances would be under licenses from the innovator company) under GMP conditions as would be consistent with current government intentions. (7)

Training and Infrastructure Development

45. Create or adopt a list serve of Russian health science researchers that includes all relevant persons in the Russian Academy of Sciences, the Ministry of Health and Social Development, Ministry of Education and Science, and other key state agencies related to health. This list serve could then be used to periodically inform researchers of existing opportunities for support or training, e.g., through the programs and donors listed above (with information about application or registration deadlines and web sites), and to highlight the health and research priorities of USAID/Russia. (8)

46. Programmatic support to ensure that the appropriate infrastructure, attitudes, and training exist and that facilities are appropriately updated warrants early attention in any program to improve availability of modern health technologies. (6)

47. Clinical research organizations and pharmaceutical companies should be used to identify needs and means to expand existing clinical trial capacity within Russia for reproductive health products. (2, 5)

48. A broad training effort for Russians used for technical assistance assignments should be supported to provide up-to-date information about modern terminology, classifications, approved standards, and internationally recognized recommendations (e.g., WHO, IPPF, CDC) for the conduct of clinical trials. (11)

49. Fund workshops/training on clinical trial design, methodology, principles of biostatistics, data management, study analysis, medical event dictionaries, and international terminology. Such design and implementation training is essential for international acceptance of future clinical research results (1, 10)

50. Fund short-term training for staff involved in developing protocols for new Russian drug candidate clinical trials. For example, when a new product is about to enter clinical trials, provide technical assistance in study design to the local principal investigator and key study staff. Alternatively, provide short (2 to 4–week) trips to host institutions (e.g., FHI, WHO, CONRAD, and others) to develop protocols. (10)

51. Support development of GCP Phase 1 (safety) capabilities within one or more institutes to support microbicides research during the next year. This would benefit

Russia as new products are developed in Russian laboratories and become ready for early clinical testing, done to international standards. (4)

52. Support workshops/training for both researchers and institutional review boards about research ethics in the conduct of clinical trials. (10, 4)

53. Implement a certification program to ensure individuals, laboratories, and clinics involved in drug development research are in compliance with international quality standards. (6)

54. For existing training programs in GLP, GMP, and GCP, it might be sufficient for USAID/Russia to help publicize these existing opportunities and cover the cost of attendance by trainees selected by USAID/Russia. It might also be cost effective for USAID/Russia to collaborate with the CDC, FDA, or others to cover the costs of expanding the existing sessions, or to cover the costs of additional sessions for trainees that USAID has selected. (8)

55. Support in-country presentations by international contract research organizations and professional organizations for instruction in GMP, GCP, and GLP, and in the conduct and management of drug development programs. CROs with in-country representation and the Drug Information Association are resources for these workshops. (6)

56. Translate FHI's Research Ethics Curriculum into Russian, with subsequent training and dissemination. (4, 10)

57. Biostatistical training specific to the design and analysis of contraceptive trials is important for institutions involved in developing their own drug development research studies. To accomplish this training, consider establishing a collaborative relationship with an international organization, or perhaps using the model of the ICSSC. (4, 10)

58. Support English language programs especially for key investigators in clinical trials. Limited knowledge of English makes attending international conferences and seminars less valuable; it also complicates dissemination of results in international journals. (4)

59. Fund continuing education and training in reproductive health (family planning, HIV/STI treatment and prevention). (4)

60. Since support from the Russian government for education in technical and scientific fields still appears to be sufficient at the undergraduate and graduate levels, efforts by USAID/Russia to advance policy and program changes that would increase or optimize career opportunities at Russian research institutes would be very worthwhile. (8)

61. It may be possible for USAID/Russia to facilitate collaborations between investigators that qualify for the nonproliferation programs and investigators who do not qualify through communications (e.g., list services) to inform health researchers

about the current participants and activities in these programs, as well as future opportunities to submit proposals. If the number and qualifications of eligible participants is ever reviewed, it may be useful for USAID to contribute to this discussion. (8)

62. Since entrepreneurial activities are extremely important in allowing some institutes to continue their health-related early stage research programs, it would be very useful for USAID/Russia to identify and address gaps in existing programs that provide technical assistance in business management and commercialization of product or service leads, so these entrepreneurial efforts can be expanded where appropriate. (8)

APPENDICES

A. SCOPE OF WORK

B. ORGANIZATIONS VISITED AND STAFF CONTACTED

C. NOTES REGARDING ORGANIZATIONS, PERSONS VISITED, PROGRAMS, AND POTENTIAL PRODUCTS

D. ORGANIZATION CAPABILITIES

E. ORGANIZATION SOURCES OF FUNDS

F. PROCEDURES FOR DRUG REGISTRATION

G. REFERENCE MATERIALS

APPENDIX A

SCOPE OF WORK
(from USAID)

SCOPE OF WORK, March 2005

Assessment of Potential Collaborations in the Research and Development of New Reproductive Health Technologies Between Existing USAID–Sponsored Programs and Biomedical Research Institutions in Russia

I. BACKGROUND

As part of a new five-year development strategy, USAID/Russia is exploring ways of more closely aligning USAID development programs inside Russia with other important and strategic USAID–financed foreign assistance programs, especially those that are relevant and important in biomedical and public health research.

The USAID research program in the Bureau for Global Health also has a special interest in supporting the next generation of life-saving health technologies through partnerships between United States and local Russian institutions. To this end, it would be useful to consider how such partnerships could contribute to USAID goals in the research and development (R&D) of reproductive health (RH) products including new or improved contraceptive products to prevent or reduce unwanted pregnancies, as well as new products such as microbicides that would prevent or reduce the sexual transmission of HIV and other sexually transmitted infections (STIs).

II. RESEARCH, DEVELOPMENT, AND PROVISION OF NEW AND IMPROVED CONTRACEPTIVES

For more than two decades USAID has been recognized as a global leader in the field of contraceptive research and development. USAID has played an important role in the development, testing, and regulatory approval of many contraceptive products available in the market today, including low-dose oral contraceptives, the CuT 380A IUD, Norplant and Jadelle implants, novel female barriers, and other methods of family planning (FP). In addition, USAID has played a key role in improving the provision and use of these and other methods (such as Depo-Provera) throughout the world. USAID also plays a unique leadership role in ensuring the high quality of contraceptives that it provides worldwide. Family planning and reproductive health programs face many new questions and challenges during the next decade. The demand for safe, effective, acceptable, and affordable contraceptives and disease prevention technologies will continue to grow as millions more young women and men throughout the world reach reproductive age.

USAID supports a broad portfolio of research activities which cover the continuum from the conception of an idea or approach through the use of the final technology by a client in a family planning and reproductive health program. These activities include:

Identification and Preclinical Research of New Contraceptive Leads - The increased knowledge of reproductive biology and advances in molecular biology and other disciplines are being used to identify new contraceptive product leads. Some currently available methods may also need to be modified and improved to make them safer as

more is learned about the risks associated with their long-term use. In some cases, it may also be possible to improve product effectiveness through better formulation technology.

Clinical Testing of New and Improved Contraceptives - Clinical trials with appropriate volunteers are needed for all new contraceptive products to assess their safety, acceptability, and effectiveness in preventing or reducing the risk of pregnancy.

Acceptability and Introduction Studies - No single method is likely to meet the contraceptive and reproductive health needs of every woman or man. In addition to safety and effectiveness, duration of action, availability, convenience, stage of reproductive life, and affordability also play a role in determining the technologies that are made available and that an individual or couple selects and uses. Contraceptive and other reproductive health decisions are also strongly affected by culture, public health and health care policies, and service delivery characteristics in the country where the individual or couple lives.

Technology-Related Program Research - Additional training and technical support are needed to strengthen service programs and enable them to provide contraceptive and disease prevention methods to the most people, in the most appropriate ways, and with limited resources, given the health, social contexts, and risk factors of the clients. Many service programs need to address questions such as: How can family planning programs provide prevention, diagnosis and/or treatment for STIs? Conversely, how can HIV/AIDS programs provide appropriate contraception? How can service providers best address the reproductive health needs of various target groups, prevent unsafe abortion, and mitigate other chronic health conditions that affect the quality of life of many women and men? Cost and sustainability research is also needed to identify what program options are possible, define what resources are needed, and inform subsequent programmatic decisions.

Post-Introduction Surveillance and Epidemiological Studies - Questions of interest address issues such as: How do contraceptives affect the acquisition and progression of HIV/AIDS? What is the impact of different hormonal contraceptives on reproductive cancers, bone density, and other health parameters, etc.? Assurances that contraceptive methods are safe must be made on the basis of sound research. Efforts are also needed to define and better meet the contraceptive and other reproductive health needs of groups that have traditionally received less attention from family planning programs. These groups may need to be reached through nontraditional approaches. Pregnancy, unsafe abortion, and a variety of STIs are among the many reproductive health risks that confront growing numbers of young people in many countries. In addition, reproductive health technologies may affect young people differently than adults and the acceptability and affordability of these technologies may also differ.

Quality Assurance of Reproductive Health and Related Technologies - In addition to developing and improving new reproductive health technologies, it is critical that the quality of these technologies is monitored worldwide to meet high international standards. USAID has supported the development of facilities and techniques to evaluate the quality of contraceptive products and has helped define the international standards used for this testing. Research is also needed to develop quality assurance methods for other reproductive health products such as STI test kits, antiretroviral therapies (ARTs),

and other diagnostic and therapeutic products. There is a need to develop simple quality assurance tests that can be performed at developing country sites inexpensively and efficiently. This involves building local capacity for monitoring product quality, as well as providing the appropriate technologies for these programs.

III. MICROBICIDE RESEARCH AND DEVELOPMENT

Because current strategies for preventing sexual transmission of HIV, such as condom use by the male partner, are often not available options for many women, USAID is actively developing vaginal microbicides as a female-controlled chemical barrier to HIV. For more than a decade, USAID has supported the biomedical and behavioral research that is needed for the successful development of such products. These efforts have yielded several promising candidates, some of which are now or soon beginning the final stages of clinical testing in international trials for their safety, acceptability, and effectiveness in preventing or decreasing sexual HIV transmission.

USAID has collaborated with the National Institutes of Health, the Centers for Disease Control and Prevention, and the Food and Drug Administration to develop the U.S. Government Strategic Plan for Microbicides. The objectives of this plan and USAID–sponsored activities include:

Preclinical Development and Evaluation of Potential Microbicide Leads - A broad spectrum of early stage research is needed to support the discovery, characterization, and subsequent development of potential new active agents for use in microbicides.

Formulation and Delivery of Potential Microbicides – Given the identification of promising new active agents, it is essential to develop and assess safe, acceptable, and effective formulations and modes of delivery for microbicides, applying knowledge from the chemical, pharmaceutical, physical, bioengineering, and social sciences.

Clinical Testing of Microbicides – Extensive clinical trials will be needed with appropriately selected volunteers to assess the clinical safety, acceptability, and effectiveness of new microbicides in reducing the transmission of HIV and other STIs (and preventing pregnancy for products that are also contraceptive) in developing countries and the U.S..

Identification of Behavioral Factors and Social Science Issues – Behavioral and sociological research is needed to enhance microbicide development and testing, and to better understand factors that will affect future microbicide use and acceptability in developing countries.

Provision of Training and Infrastructure – Significant capacity building is needed to establish, maintain, and strengthen the appropriate training and infrastructure needed to conduct microbicide research internationally and to accelerate future access to microbicides in diverse populations and settings.

IV. PURPOSE OF ASSESSMENT

The purpose of this Assessment is to have a team of relevant experts examine the feasibility of more closely and effectively linking the USAID/Russia health and infectious disease programs with the USAID Bureau for Global Health programs in contraceptive and microbicide research and development, as well as related reproductive health research. The Assessment will attempt to identify the specific means by which biomedical and other scientists in Russia could collaborate more effectively with on-going USAID efforts to address various reproductive health objectives, especially those that are described above in Sections II and III. The Assessment will also collect preliminary information on which investigators, institutions, and types of research could be most effectively matched with the ongoing USAID efforts in this area, as well as identify criteria and strategic suggestions for additional collaborative opportunities between USAID and Russian scientists and institutions in the future. This Assessment will primarily be used to collect information, ideas, and suggestions. The implementation of any recommendations arising from this effort will depend on future decisions and resources.

V. QUESTIONS TO BE ADDRESSED

This Assessment will address the following Key Questions.

1. Are there opportunities in Russia for USAID to advance the research objectives listed above in Sections II and III? If so, what are the most promising and highest priority opportunities in this area?

2. In particular, are there Russian institutions, e.g., that presently provide clinical health care or conduct clinical research, that have sufficient capacity, experience, and interest to conduct clinical trials of new contraceptives, microbicides, or other reproductive health technologies?

3. What data are available regarding populations in Russia from which potential volunteers could be recruited for clinical trials of new contraceptives, microbicides, or other reproductive health technologies? For what phase of clinical trials, e.g., for safety, expanded safety, or effectiveness in preventing pregnancy or HIV infection, etc., are suitable populations and clinical research sites available? Are there populations and sites that would be suitable to evaluate effectiveness of contraceptives or microbicides in preventing other STIs?

4. If appropriate sites and populations are available, what opportunities, e.g., with which institutions, which trial phases, and which endpoints, etc., could be most productively pursued in the next year? What is the potential for conducting clinical studies on new contraceptives or microbicides, etc., in Russia in the future?

5. What is the regulatory environment for clinical trials as well as other stages of research and development for reproductive health technologies in Russia? For example, what are a) the administrative requirements for approval, conduct, and

oversight of research (including local ethical and scientific review, central review, requirements for import of products for clinical research, etc.), b) the extent of ethics and Good Clinical Practice training at various locations, c) the ability to perform research of adequate quality to use for product registration, d) the restrictions on export of preclinical and clinical specimens and/or data for use by collaborating parties? Are there constraints on intellectual property rights that potential collaborators need to be aware of?

6. Are there specific technologies or technical programs in Russia that are linked to commercial channels and capacity that could not only advance research on new contraceptives, microbicides, or other reproductive health technologies, but promote future manufacturing and/or distribution (inside or outside of Russia) of such products as well?

7. Are there particular existing institutions or private sector commercial entities in Russia that could be considered as potential and advantageous partners for manufacturing of new contraceptives, microbicides, or other reproductive health technologies, including their formulation, delivery systems, packaging, or related materials, etc., especially for provision of such products through public sector programs in developing country and low resource settings?

8. Are there opportunities to collaborate on early stage technology research and preclinical product development that would advance reproductive health interests in Russia?

9. What behavioral and social science research, including acceptability of products and services, could be advanced by collaborative efforts and contribute to developing new technology, strengthening service delivery programs, and improved reproductive health?

10. What efforts are needed and possible to build research capacity in any area contributing to improved reproductive health in Russia?

11. What is the current and future potential to use capacity and expertise already existing in Russia to provide technical assistance, training, service delivery, and other contributions to advance reproductive health services and research programs in developing countries, e.g., in Africa?

12. Are there other ways, not included above, that USAID could use the scientific community in Russia to advocate, support, and advance reproductive health research programs?

13. What types of financial and other investments would be needed to pursue any opportunities in the above areas, and by whom?

14. What types of collaborations could be established in the next year and productively implemented in the next 2-5 years?

VI. ASSESSMENT TEAM COMPOSITION

The Assessment Team will include three or four experts in the research and development of reproductive health technology. This will include a USAID staff person who is familiar with the contraceptive and microbicide research and development programs sponsored by the Bureau for Global Health, as well as by other U.S. Government agencies and other donors or sponsors. The Assessment Team will also include at least one medical clinician currently working with existing USAID–funded contraceptive and microbicide projects to develop new clinical research sites and to implement clinical studies to evaluate safety and effectiveness of current product leads at those sites. The selection of a Assessment Team Leader will be determined after the individual Assessment Team members have been finalized.

The technical expertise represented in the composition of the Assessment Team will be intentionally weighted to emphasize the technical assessments needed to address the Key Questions focusing on clinical trials research, but it is also intended that Assessment Team members address each of the other Key Questions as thoroughly as possible within the scope of their expertise. This will focus the greatest technical expertise of the Assessment Team on the potential for conducting contraceptive and microbicide clinical trials in Russia, since such trials are a great programmatic and technical need in the next year (especially for microbicides), while collecting and evaluating information on other opportunities to support research on reproductive health technology and services as well. For example, it will also be very important to assess the potential to collaborate on advancing promising product leads that are still at the preclinical stage of development, as well as later stage needs such as capacity for manufacturing, packaging, and distribution of products. Therefore, it is expected that the Assessment will include appropriate materials and opportunities, e.g., for briefings, meetings, and site visits, to assess all of the Key Questions to the greatest extent possible.

USAID/Russia will have two full-time bilingual Russian specialists on the Assessment Team including a health researcher and a program manager with experience in promoting public/private sector collaborations.

VII. METHODS AND SCHEDULE

The schedule should allow the Assessment Team at least one day to review an initial package of briefing materials provided by USAID and the Civilian Research and Development Foundation (CRDF).

The visit to Russia is planned as a one to two-week in-country assignment, with a number of site visits to relevant research facilities located in Moscow and Moscow Oblast, and with two or more trips for site visits within the European part of Russia and Siberia (e.g., to St. Petersburg).

CRDF has already worked extensively with various U.S. government entities and scientists at Russian institutions to establish other joint research efforts in the prevention and treatment of HIV/AIDS, STDs, tuberculosis, hepatitis, and other diseases. It is planned that CRDF will be instrumental in identifying the individual investigators and

institutions that will be most useful for the Assessment Team to visit.

Approximately three weeks will be allocated for the Assessment Team to prepare the Final Report. The Final Report is expected to be a 10 to 15-page document containing recommendations and strategic priorities for research in reproductive health technology and that responds as clearly and unambiguously as possible to the Key Questions above. To the extent possible, the Final Report should suggest future programmatic, staffing (level of effort), and funding requirements needed to launch credible new initiatives in this area, and identify the specific Russian institutions and existing USAID Cooperating Agencies with which promising partnerships can be established. The Final Report will be due April 15, 2005.

VIII. INFORMATION SOURCES

Information resources will be shared with the Assessment Team by USAID/Russia, USAID/Washington, CRDF, individual Assessment Team members, and other possible sources.

IX. FINAL REPORT AND DISSEMINATION

The Final Report will include an overall assessment of the Key Questions listed in Section V above. Other information to be included in the Report will be determined in consultation with USAID/Russia staff before and during the Assessment. The Final Report will be submitted to USAID/Russia on diskette in MS Word along with three hard copies. The structure and format of the Report will be proposed by the Assessment Team and an outline for the Report will be approved by USAID/Russia/OH staff at the beginning of the Assessment.

X. BUDGET

An estimated Budget for this Assessment is attached.

PD&S funds will be used to finance this Assessment. The assigned staff from USAID/Russia will be funded from their contracts as needed. The time and effort of Assessment Team members that are employees of USAID or USAID CAs will be covered by their existing support. Assessment Team Members who are Consultants will be supported through subcontracts with the POPTECH Program.

APPENDIX B

ORGANIZATIONS VISITED AND STAFF CONTACTED

ORGANIZATIONS VISITED AND STAFF CONTACTED

MARCH 14–23, 2005

MOSCOW

1. USAID/MOSCOW

Address and contact information:

19/23 Novinsky Blvd.
121099 Moscow, Russia
Phone: 7-095-728-5000

Staff persons interviewed:

Nikita Afanasiev, MD, MPH, Senior Infectious Disease Advisor, Office of Health. E-mail: nafanasiev@usaid.gov
Betsy Brown, Director, Office of Health. E-mail: bebrown@usaid.gov
Nicole R. Judice, Technical Advisor for Policy Central Research Institute for Skin and Venereal Disease, University of Michigan Population Fellow. Phone: 7-095-964-4653, E-mail: judice1@msn.com
Ludmila Maximova, Foreign Commercial Service, Legal Advisor on Pharmaceutical Industry in Russia
Alexey Savinykh, HIV/AIDS Officer, Office of Health. E-mail: asavinykh@usaid.gov
Robin Solomon, Consultant
Michael V. Stepanov, Project Management Specialist (accompanied assessment team on site visits)
Ludmila Vassilieva, Interpreter. Phone: 7-095- 401-5271, Cell phone: 7-095-567-7573

2. MOSCOW MEDICAL ACADEMY

Address and contact information:

Malaya Trubetskaya 8, Building 2
119881Moscow, Russia
Phone: 7-095-248-0553/248-3122/248-4777, E-mail: ID@mmascience.ru

Staff persons interviewed:

Sergey Vital'yevich Grachev, Provost for Science, MMA
Lyudmila V. Mikheeva, Head of International Department

3. RUSSIAN ASSOCIATION FOR PREVENTION OF SEXUALLY TRANSMITTED DISEASES (SANAM)

Address and contact information:

13 Ul. Dovatora
119048 Moscow, Russia
Phone: 7-095-246-8645, 245-5470, 245-4789

Staff persons interviewed:

Sergey F. Dubovsky, Acting Director General. E-mail: dsf@comtv.ru; sanamclinic@comtv.ru
Artyom Gill, Epidemiologist. E-mail: artyom5@mail.ru

4. IVANOVSKY INSTITUTE OF VIROLOGY, NATIONAL RESEARCH CENTER INSTITUTE OF IMMUNOLOGY

Address and contact information:

Gamaleya St. 16
Box 15
127562 Moscow, Russia
Phone: 7-095-190-3048

Staff persons interviewed:

Edward V. Karamov, Head, Laboratory of Molecular Biology of HIV, Head, Lab of Immunochemistry. E-mail: karamov2004@yandex.ru
Igor G. Sidorovich, Head of AIDS Department. Phone: 7-095-117-8100, E-mail: sidorovich@newmail.ru

5. INSTITUTE OF PROTEIN RESEARCH, RUSSIAN ACADEMY OF SCIENCES

Address and contact information:

Institutskaya St. 4
142290 Pushchino
Moscow Region, Russia
Phone: 7- 0967- 632-7871

Staff persons interviewed:

Yury V. Mitin, Director
Sergey A Potehin, Head, Laboratory of Thermodynamic of Biopolymers

6. BIOLOGICAL TESTING LABORATORY, SHEMYAKIN & OVCHINNIKOV INSTITUTE OF BIOORGANIC CHEMISTRY, RUSSIAN ACADEMY OF SCIENCES

Address and contact information:

Prospekt Nauki, 6
142290 Pushchino
Moscow Region, Russia
Phone: 7-0967-73-37-53, Web site: www.fibkh.serpukhov.su

Staff person interviewed:

Arkady N.Murashev. Head, Biological Testing Laboratory. E-mail: murashev@fibkh.serpukhov.su

7. INSTITUE OF PHYSIOLOGY AND BIOCHEMISTRY OF MICROORGANISMS, RUSSIAN ACADEMY OF SCIENCES

Address and contact information:

Prospekt Nauki, 5
142290 Pushchino
Moscow Region, Russia
Phone: 7-0967-73-29-79/73-16-92

Staff persons interviewed:

Roman V. Borovik, Director, Research Center for Toxicology and Hygenic Regulation of Biopreparations. E-mail: toxic@online.stack.net
Vera A. Dmitrieva, Executive Director, Center for Ecological Research and BioResources Development. E-mail: vdmitrieva@ibpm.pushchino.ru
Felix P. Filatov, Principal Scientist; Project Manager, Research Center for Toxicology and Hygenic Regulation of Biopreparations. E-mail: toxic@online.stack.net
Olga A. Stepnaya, Senior Researcher. E-mail: stepnaya@ibpm.pushchino.ru

8. RESEARCH CENTER OR OBSTETRICS, GYNECOLOGY AND PERINATIOLOGY, RUSSIAN ACADEMY OF MEDICAL SCIENCES (ALSO KNOWN AS CENTER FOR MATERNAL AND CHILD HEALTH)

Address and contact information:

Akademika Oparina 4
Moscow
Phone: 7-095-298-2157

Staff persons interviewed:

Olga G. Frolova, Head, Dept of Medico-Social Research
Zhana Gorodnicheva, Research Assistant, Department of International Research Programs
Vladimir I. Kulakov, Director, Research Center of Obstetrics, Gynecology and Perinatology; Vice President of the Russian Academy of Medical Sciences
Vera N Prilepskaya, Head, Outpatient Department
Svetlana Rogovskaya, Obstetrics/Gynecology Consultant, Outpatient Department

9. RESEARCH CENTER OF MOLECULAR DIAGONOSTICS AND THERAPY

Address and contact information:

Simpheropolsky Blvd. 8
117638 Moscow, Russia
Phone: 7-095-113-2351/113-2365/113-1225/248-2163

Staff persons interviewed:

Alexei Federov
Evgenii S. Severin, General Director; Head, Department of Biochemistry. E-mail: e.severin@mtu-net.ru

Peter G. Sveshnikov, Deputy Director. E-mail: svesh@aha.ru

10. INSTITUTE OF PHYSICAL–CHEMICAL MEDICINE

Address and contact information:

Malaya Pirogovskaya Ul.
119992 Moscow, Russia
Phone: 7-095-246-4311/246-7721

Staff persons interviewed:

Vadim M. Govorun, Deputy Director. E-mail: govorun@hotmail.ru
Vassily N. Lazarev, Head of Laboratory

11. G. GAUZE STATE INSTITUTE FOR NEW ANTIBIOTICS, RUSSIAN ACADEMY OF MEDICAL SCIENCE

Address and contact information:

Bolshaya Pirogovskaya, 11
119021 Moscow, Russia
Phone: 7-095-245-3753/246-9980/726-4272/245-0154

Staff persons interviewed:

Alexander A. Firsov, Head, Department of Pharmacokinetics and Pharmacodynamics
E-mail: firsov@dol.ru
Maria N. Preobrazhenskaya, Deputy Director. E-mail: mnp@space.ru

12. MOSCOW REGIONAL INSTITUTE OF OBSTETRICS AND GYNECOLOGY

Address and contact information:

Pokrovka, 22a
Moscow, Russia
Phone: 7-095-924-6282

Staff persons interviewed:

Elena Bulycheva, Head of Family Planning Center. Cell phone: 8-916-924-0630
Lela R. Kavtaladze, Head of International Liaison Department. Cell phone:
7-095-136-8793, E-mail: kavteladze@mail.ru

13. CENTER OF MODERN MEDICAL TECHNOLOGY (TEMPO)

Address and contact information:

M. Trubetskaya, 8
111981 Moscow, Russia
Phone: 7-095-708-3954/708-3951

Staff persons interviewed:

Natalia Popova, TEMPO Associate
Yuri V. Remnev, Deputy Director. E-mail: remnevYV@yandex.ru, remnev@nptemp.ru

14. InfaMed (and Prevention, an NGO)

Address and contact information:

Box 46
123056, Moscow, Russia
Phone: 7-095-208-3159

Staff persons interviewed:

Yuri S. Krivoshein, President
Igor V. Smirnov, Head of Medical Department. Phone: 7-095-324-8209,
E-mail: i_sm@mail.ru

ST. PETERSBURG

Elena Frolova, Interpreter. Cell phone 8-812-939-4669

15. OTT INSTITUTE OF OBSTETRICS AND GYNECOLOGY, RUSSIAN ACADEMY OF MEDICAL SCIENCES

Address and contact information:

Mendeleevskaya Linia, 3
199034 St. Petersburg, Russia
Phone: 7-812-328-9824/328-9833/328-9889/328-9843/328-9812

Staff persons interviewed:

Igor Kogan, Scientific Secretary. E-mail: ikogan@mail.ru
Marina Tarasova, Deputy Director. E-mail: tarasova@ott.ru
Alevtina M. Savicheva, Head, Microbiology Laboratory. E-mail: savicheva@mail.ru
Sergey Selkov, Head, Laboratory of Immunology. E-mail: selkovsa@mail.ru

16. PAVLOV STATE MEDICAL UNIVERSITY

Address and contact information:

Lev Tolstoy St., 6/8
197089 St. Petersburg, Russia
Phone: 7-812-238-7023/238-7153/238-7058/238-7166

Staff persons interviewed:

Dmitry Lioznov, Director, Center for Preventive Medicine. E-mail: lioznov@spmu.rssi.ru
Malikov, Director, Clinical Trials Unit
Tatyana Medvedeva, Member, Ethical Committee
Edwin Zvartau, Vice-Rector for Research. E-mail: zvartau@spmu.rssi.ru

17. STATE RESEARCH INSTITUTE OF HIGHLY PURE BIOPREPARATIONS

Address and contact information:

Pudozhskaya St. 7
197110, St. Petersburg, Russia
Phone: 7-812-230-4438/48-88; Web site: www.hpb-spb.com

Staff persons interviewed:

Sergey A. Ketlinsky, Deputy Director in Science. E-mail: ketlinsky@inshpb.spb.ru
Kolobov, Head, Lab of Synthetic Peptides
Andrey S. Simbirtsev, Head, Laboratory of Immunopharmacology. E-mail: smbirtsev@hpb.spb.ru, sim@inshpb.spb.ru

18. INSTITUTE OF CYTOLOGY, RUSSIAN ACADEMY OF SCIENCES

Address and contact information:

Tikhoretsky Prospekt 4
Phone: 7-812-247-44-96

Staff person interviewed:

Tamara V. Beyer, Head of Research Group
Sergei N. Borchsenius, Head of Genome Structural Organization
Valeri A. Pospolov, Head of Laboratory of Molecular Mechanisms of Cell Differentiation
Sergei O. Skarlato, Deputy Director for Science and Head of Laboratory of Unicellular Organisms

19. THE BIOMEDICAL CENTER

Address and contact information:

Pudozhskaja St. 7
197110 St. Petersburg, Russia
Phone: 7-812-230-4872/542-8311

Staff person interviewed:

Andrei P. Kozlov, Director. E-mail: biomed@mailbox.alkor.ru, contact@biomed.spb.ru.

20. STELLIT

Address and contact information:

Bumazhnaya St. 9, Suite 617
190020 St. Petersburg, Russia
Phone: 7-812-445-28-93, Web site: www.spbstellit.ru

Staff persons interviewed:

Larisa Gareeva, Project Manager. E-mail: lagar@bk.ru.
Maia Rusakova, Director. E-mail: maia_socio@hotmail.com, maia@spbstellit.ru

21. YUVENTA

Address and contact information:

Petrergovskyi Pr-t, 12
St. Petersburg, Russia
Phone: 7-812-251-4258

Staff person interviewed:

Pavel N. Krotin, Director

APPENDIX C

NOTES REGARDING ORGANIZATIONS, PERSONS VISITED, PROGRAMS, AND POTENTIAL PRODUCTS

NOTES REGARDING ORGANIZATIONS, PERSONS VISITED, PROGRAMS, AND POTENTIAL PRODUCTS

Information contained in this appendix was obtained from documents provided by the respective institution, from Civilian Research and Development Foundation (CRDF) staff and from notes of the assessment team members. As such, there is a degree of subjectivity and, while instructive and accurate to the best of our efforts, these comments are not necessarily comprehensive.

MOSCOW MEDICAL ACADEMY

Staff persons interviewed:

Sergey Vital'yevich Grachev, Provost for Science, MMA
Lyudmila V. Mikheeva, Head of International Department

The I.M. Sechenov Moscow Medical Academy (MMA) is the oldest and the largest national medical higher educational institution, with over 1,000 medical faculty, and over 500 researchers in six research institutes. The team was briefed about research and testing facilities that MMA has available, what MMA is doing in reproductive health and what their general relevant research interests are. They mentioned a broad interest in contraception research from preclinical to clinical research. They have five clinics providing obstetric/gynecological services, one of which serves the "highest levels" and which was visited by Hillary Clinton, and four others affiliated with various MMA hospitals including a perinatal clinic providing PMTCT services. We did not visit any of these clinics or get figures on patient volume. We were told that the MMA has excellent modern microbiology laboratories established, in part, with funding from the Soros Foundation, and the clinical laboratory collaborates on International Science and Technology Center (ISTC) projects. However, we did not visit any of these laboratories. MMA has not yet been involved in clinical trials of microbicides, but expressed an interest in doing so. They are trying to set up a new research core trained in GCP, GMP, and GLP. They mentioned many staff had been trained at the Harvard School of Public Health.

MMA is a WHO Collaborating Centre for tuberculosis and malaria. Within this context, they have specialists trained in compliance for international research standards. The Institute on Tuberculosis created a special laboratory for tuberculosis and HIV/AIDS. Given the high prevalence of tuberculosis in Russia, the MMA could be an organization through which clinical studies of new products could be conducted. (We did not discuss other organizations working on tuberculosis, or what projects the U.S. Government may already have in this area.)

MMA also has a training department specialized in identifying potential, excellent research and pedagogical staff who could be trained and nurtured to be future faculty. Over 15 years, they have trained about 550 staff, with many of these individuals having also received one year of training in a foreign, developed country center of excellence (for example in the United States or the United Kingdom). The question of whether this training department could be drawn upon for any collaboration was not pursued during our meeting.

RUSSIAN ASSOCIATION FOR PREVENTION OF SEXUALLY TRANSMITTED DISEASES (SANAM)

Staff persons interviewed:

Sergey F. Dubovsky, Acting Director General.
E-mail: dsf@comtv.ru, sanamclinic@comtv.ru
Artyom Gill, Epidemiologist. E-mail: artyom5@mail.ru

SANAM is the oldest independent organization in Russia providing treatment and counseling for sexually transmitted diseases. Since their founding in 1990, they have focused on providing outreach and services to high-risk individuals. They have also conducted behavioral research among these different high-risk groups. SANAM is comprised of two units: a Prevention Unit and a fee-for-service clinic.

USAID and CDC have supported activities of the Prevention Unit: an outreach project through which SANAM reaches vulnerable populations. They have gathered impressive statistics on STI prevalence among high-risk sex workers. These individuals have a very high prevalence of syphilis, chlamydia, gonorrhea, trichomoniasis, and a rising prevalence of HIV and hepatitis B. SANAM has collaborated with CDC on behavioral aspects of prevention, and CDC has provided clinical training to their staff. They have collaborated with CDC to develop a guide to be used for training.

SANAM runs a fee-for-services clinic through which they do laboratory diagnosis, counseling, and treatment of HIV and other STIs. The fee-based clinic helps to offset some of their costs for research and to support activities of Prevention Unit during gaps in USAID/CDC funding.

During our meeting, SANAM staff described several areas of interest: 1) to increase the number of high-risk target groups for outreach work; 2) to share accumulated experience and provide training in outreach work, counseling and medical care of different groups of population at high risk of HIV and other STIs; and, 3) to conduct clinical trials in the area of HIV and other STIs (although they appear to be less interested in this area than in their behavioral research).

SANAM was an impressive organization—small but effective. The population of sex workers in Moscow is large and in demand. SANAM currently has a small cadre of outreach workers who focus on motivation and referrals to the clinic where these women then receive behavioral counseling and diagnosis and treatment. The number of outreach workers could easily be enhanced to expand their reach and impact. Also, SANAM does not provide any contraceptive services (other than condoms) but refers to other sites for these services. (They said there is only one nonstate clinic in Moscow called "East-West Foundation" that has integrated services.)

There are certain barriers for conducting clinical trials at SANAM. It is a clinical research-naïve site where most of the staff are not trained in GCP and research ethics. The license to conduct clinical trials must be obtained from the MOH if the center begins to conduct clinical trials. Since only about six clinics in Russia have been licensed to

conduct clinical trials in the area of obstetrics/gynecology (most of them are leading research institutes in this area), it is not clear how easy it would be for SANAM to obtain such a license. For behavioral research, they have used the Moscow Dental School #3 IRB and CDC's IRB to review and approve protocols. It is assumed they could use the former for clinical trials, as well.

Potential areas for collaboration and support:

- Excellent outreach model that can be replicated elsewhere
- Expand outreach to other hard-to-reach groups
- Use staff to train other organizations to do outreach, counseling and clinical services, including teaching physicians in HIV counseling and awareness
- Conduct behavioral research on the bridge population between intravenous drug users and the general population to expand knowledge of this group and develop prevention approaches
- Potential site for a project on integration of family planning and/or tuberculosis services into existing HIV programs
- Potential site in a multicenter effectiveness trial for contraceptives or for preventing STIs other than HIV. Evaluation of oral microbicides (testing of vaginal microbicides is problematic due to high rates of intravenous drug use among the population), or long-acting delivery systems for microbicides (given the conditions in which the high-risk sex worker population works in Moscow, testing of single-use short-delivery systems, such as applicators filled with a gel, does not seem realistic). Note: At this stage, they probably do not have access to a population with sufficient incidence of HIV to participate in HIV prevention trials.

IVANOVSKY INSTITUTE OF VIROLOGY, NATIONAL RESEARCH CENTER INSTITUTE OF IMMUNOLOGY

Staff persons interviewed:

Edward V. Karamov, Head, Laboratory of Molecular Biology of HIV; Head, Lab of Immunochemistry. E-mail: karamov2004@yandex.ru

Igor G. Sidorovich, Head of AIDS Department. Phone: 7-095-117-8100, E-mail: sidorovich@newmail.ru

Ivanovsky is the first laboratory in Russia working on HIV. They are a WHO reference center and have developed diagnostics (based on viral isolates). They also mentioned having developed a derivative of AZT. They are currently involved in anti-viral (including anti–HIV), vaccine-based approaches and in developing peptide fragments with potential as microbicides. In reproductive health, the Ivanovsky Institute can collaborate in research and preclinical testing of novel preparations. The lab has a broad panel of eukaryotic cell lines, including lines of human origin which can be used to test toxicity of candidate compounds. Two grant applications are now being considered (one by BTEP, the other by CRDF). The institute can partake as partners at all stages of work, in cooperation with the Moscow AIDS Center, State Institute of Immunology, and a few NGOs.

These investigators are very accomplished scientists. They have ten patents on antiviral drugs and are now working on fusion inhibitors similar to the leads at major pharmaceutical companies. They have experience or interests in using genetically engineered Lactobacillus or E. coli to produce antimicrobial or therapeutic peptides. They also mentioned a number of ideas or leads for microbicidal agents including PMPA, CD4–derived peptides, sulfated polysaccharides, and chitosans; although it was not clear that they are actively working on all of these themselves. They have, however, identified and decoded the structure of a compound from garlic that inhibits viral integration, and are working with chemists on novel antiviral flavenoids from plants. They are able to do in vitro screening for anti–HIV activity and are also interested in formulation and delivery. Overall, they were quite aware of the key issues and leads in microbicide development. They have some publications in English language journals from the early 1990s. They identified their biggest challenges as the lack of state support for research and the regulatory reforms needed to allow collaborations and clinical testing of new products. For current funding, they have to use their own fees and salaries, and it appears that their institute has some income from a few animal products, including diagnostic items for hantu and west Nile virus. They have also used their personal contacts with some past success to influence the Russian parliament to support research, and hope to make new initiatives of this type in the future. They are aware of or are participating in some industrial collaborations but it appears there is little interest in these fields from the for-profit private sector, in Russia or internationally. They have a number of clinical collaborators they have worked with in the past or could work with in the future. They also have some expertise in intellectual property issues and national regulations for clinical trials. They mentioned a clinical collaboration they had planned with the Ott Institute in St. Petersburg and the Moscow Institute of Skin and Venereal Diseases, neither of which were funded. They feel stymied by the absence of national leadership on the need for HIV programs and the need for Russian research and industry to adopt international standards. They have been able to travel to international meetings. They have already had some experience with NIH, ISTC, BTEP, CRDF, and are aware of IPM. They cited many staff losses in recent years, including 22 staff members that have moved to the United States and are now working for private companies, and one who is on the faculty at George Washington University.

Potential product candidates

- Peptide fusion inhibitors (basis of a possible collaboration with GSK)
- Reverse transcriptase inhibitors (The institute applied to CRDF for a project on PMPA [TDF] derivatives)
- Vaginal ring and biomolecular polymeric delivery systems
- CD4 receptor inhibitors-sulphates, polysaccharides, peptides
- Inhibition of integrin receptors-garlic extracts
- AIDS vaccine (They mentioned that a vaccine developed at the Institute of Immunology is now in testing at VECTOR, and that funds had been requested from the Bill and Melinda Gates Foundation to work on a vaccine)

INSTITUTE OF PROTEIN RESEARCH, RUSSIAN ACADEMY OF SCIENCES

Staff persons interviewed:

Yury V. Mitin, Director

Sergey A. Potehin, Head, Laboratory of Thermodynamics of Biopolymers

Focus of their research is on synthetic peptide microbicides. The institute synthesizes antimicrobial peptides, modifies them, and assesses antimicrobial properties. The lab recently synthesized a number of arginine-containing tetradecapeptides, some of which possess high antimicrobial activity. This institute has experience with a broad range of fundamental research on protein structure, folding and synthesis, and peptide synthesis and function.

These scientists and their colleagues are in a very difficult situation for academic researchers. Pushchino has in the past been an active, well-funded, and productive center for biology and physics without warfare or military connections. Now the state can pay salaries but not support research and therefore many scientists have left. Students apparently still come to complete higher degrees, but they do not stay afterwards. Dr. Mitin explained his Soviet-era international collaborators have all passed away, and with his lack of resources (and perhaps nearing retirement) he is not pursuing new collaborators. Dr. Potehin is also a senior investigator but still has a livelier research program and has done some interesting work on new ways to synthesize proteins. He has been more effective in making international collaborations and using the available programs including INTAS (European Union), Swiss, and a collaboration in Los Angeles. He has been fortunate because collaborators have approached him and he has not had to find them. He does, however, write to conference organizers and ask them for travel funds, which he has received.

Potential product candidates

- Peptide fiber structures with anti-genes for enhanced immune responses (in collaboration with a Swiss foundation and a Swiss laboratory in Lausanne)

BIOLOGICAL TESTING LABORATORY, SHEMYAKIN & OVCHINNIKOV INSTITUTE OF BIOORGANIC CHEMISTRY, RUSSIAN ACADEMY OF SCIENCES

Staff person interviewed:

Arkady N.Murashev, Head, Biological Testing Laboratory. E-mail: murashev@fibkh.serpukhov.su

The first national good laboratory practice facility for nonclinical product development has been elaborated at the Laboratory of Biological Testing. The laboratory is the only AAALAC–approved facility in Russia. Some major tasks are conducted at the laboratory: development and maintenance of in-vitro and in-vivo experimental biomodels, preclinical safety trials of biologically active compounds (preclinical drug development), and preliminary screening of the biological (therapeutical) activity of novel substances. Under a U.S. State Department grant, this institute developed a specific pathogen free (SPF) animal production facility and, later, a preclinical toxicology screening facility. The Animals Breeding Center is a unique facility engaged in breeding and selling inbred and out-bred SPF mice and rats for research purposes. The laboratory conducts contract research for a variety of groups using mice, rats, and rabbits. They are involved in hosting international conferences on GLP and put a heavy emphasis on the

continued training of staff to ensure maintenance of accreditation.

This is clearly a world-class animal testing facility. They anticipate qualifying for several additional accreditations in 2005. They do a lot of toxicology testing under contract for Russian and non–Russian pharmaceutical and chemical companies on products from Russia and abroad. They have just renovated the facility and replaced equipment using a $1 million ISTC grant, and additional funds may be pending. The profits are adequate to cover salaries and support other work at the testing lab as well as the institute. The institute animal production facility seemed to be thriving as well. In collaboration with the U.S. FDA, the institute sponsors GLP training workshops that are very popular. There are no GLP–compliant animal feeds produced in Russia, so these are usually purchased from Germany.

INSTITUE OF PHYSIOLOGY AND BIOCHEMISTRY OF MICROORGANISMS, RUSSIAN ACADEMY OF SCIENCES

Staff persons interviewed:

Roman V. Borovik, Director, Research Center for Toxicology and Hygenic Regulation of Biopreparations. E-mail: toxic@online.stack.net
Vera A. Dmitrieva, Executive Director, Center for Ecological Research and BioResources Development. E-mail: vdmitrieva@ibpm.pushchino.ru
Felix P. Filatov, Principal Scientist; Project Manager, Research Center for Toxicology and Hygenic Regulation of Biopreparations. E-mail: toxic@online.stack.net
Dr. Olga A. Stepnaya, Senior Researcher. E-mail: stepnaya@ibpm.pushchino.ru

Within this institute, a Center for Ecological Research and BioResources Development was organized four years ago to facilitate developing research, business, and other partnerships, to guide scientists in the regulations for the conduct of regulatory studies and to facilitate all of the organization work, including obtaining permits from the government of Russia for research. They have a fulltime staff of 15, plus a network of contractors with knowledge about import/export of drugs and biologics, and all other relevant regulatory processes.

They have many international collaborators, such as institutions and companies in the United States and Britain. With Washington State University, they have a USAID grant for $2.2 million. They have a major effort in developing biological approaches to oil spill clean ups. Dr. Dmitrieva is also head of the new International Business Center with a staff of 15, and funded by a BII grant to help with commercialization of new product leads, one of which is a hantu virus vaccine. They will establish a research and innovation center at the university in Pushchino, and have a new master's degree program in business development as well. Dr. Stepnaya described a multi-enzyme preparation of microbial origin (isolated from the local river) that is active against gram negative and positive bacteria, including many common human pathogens such as staphylococcus and aspergillus. It also has antiviral and antifungal activity and has shown clinical effectiveness as a therapy for mastitis. They are actively seeking a private sector partner for further product development.

The team also met Drs. Roman V. Borovik (Director) and Felix P. Filatov (Principal Scientist) from the Research Center for Toxicology and Hygienic Regulation of Biopreparations, which is located in Serpukhov. Dr. Filatov described extensive work on promising leads for DNA vaccines against HPV, HSV–1 and 2, hanta virus, and others. He explained that DNA vaccines are attractive because they are much safer to produce than products based on whole virus, they are cheaper to manufacture, they cannot escape into the environment, their stability is greater and they do not require a cold chain, they are cheaper to deliver, they induce both humoral and cellular responses, and different DNA vaccines can be combined together. Dr. Filatov has collaborators at Ft. Detrick, Maryland, and travels there often. The center in Serpukhov is certified to do U.S. Department of Defense and U.S. Department of Agriculture contract work, and has extensive collaborations with FDA, Eli Lilly, and RAPS, to provide training in GLP, GCP, and quality assurance. They are also developing a gene-engineered L–asparaginase for leukemia therapy in collaboration with St. Jude's Hospital and United States companies.

Potential product candidates

- DNA vaccines against virus infections (herpes 2, human papilloma virus [HPV])
- Asparaginase treatment
- Lysoamidase
- Bacterial microbial enzyme vaccine
- Preclinical STI vaccine development
- An HSV 2 vaccine ready for preclinical testing in collaboration with Ivanovsky Institute

RESEARCH CENTER OF OBSTETRICS, GYNECOLOGY AND PERINATOLOGY, RUSSIAN ACADEMY OF MEDICAL SCIENCES (ALSO KNOWN AS CENTER FOR MATERNAL AND CHILD HEALTH)

Staff persons interviewed:

Olga G. Frolova, Head, Department of Medico-Social Research
Zhana Gorodnicheva, Research Assistant, Department of International Research Programs
Vladimir I. Kulakov, Director, Research Center of Obstetrics, Gynecology and Perinatology; Vice President of the Russian Academy of Medical Sciences
Vera N. Prilepskaya, Head, Outpatient Department
Svetlana Rogovskaya, Obstetrics/Gynecology Consultant, Outpatient Department

The Research Center for Obstetrics, Gynecology and Perinatology is headed by Professor Kulakov, who is also the Chairman of the Department of Obstetrics and Gynecology at the Moscow Medical Academy, as well as the Vice President of the Russian Academy of Medical Sciences. The center is an independent clinical and research center under the Russian Academy of Medical Sciences. It is a leading institute in obstetrics, gynecology, and perinatology in Russia and one of three WHO collaborating centers in human reproduction in Russia. It also serves as a clinical and teaching basis for the Sechenov Moscow Medical Academy.

A variety of clinical and research departments, labs, and units comprise the center (department of prenatal care, prevention and treatment of infertility and miscarriage, endoscopical surgery, among many). This center is licensed to conduct obstetric/gynecological clinical trials in Russia. Professor Vera Prilepskaya, who is a head of the Outpatient Unit, is currently the chair of the Obstetrics/Gynecology Expert Committee (like an advisory board) of the Pharmacological Committee, the main committee making recommendations to the government about regulatory approvals.

The Outpatient Unit has been actively involved in many clinical trials conducted by large pharmaceutical companies (among them Organon, Schering AG, Gideon Richter, Wyeth and others). These were mainly introductory trials of contraceptives that are already registered elsewhere and seeking approval in Russia (Evra, Nuva Ring, Implanon, and Diane 35). Most of the studies they have conducted are relatively small (e.g., 100 subjects). However, they collaborate with other clinics in the Moscow region and get referrals from these other centers, so are able to recruit into clinical trials on a fairly rapid basis.

They have a specific interest in contraception clinical trials in the future, as well as with studies of cervical pathology. In addition, they expressed interest in STI prevention studies, but almost certainly do not have access to the necessary population for HIV effectiveness studies. Phase I safety trials or Phase II expanded safety trials may be possible, as well as effectiveness trials for non–HIV STI prevention (CT, HPV, trichomoniasis). We visited the clinic, which was extremely active, with large numbers of patients from which to draw for clinical trials. They have experience in colposcopy, which is routinely done on all patients. They have undergone GCP audits by the various companies with whom they have conducted clinical trials.

The center does not have good support in the areas of data management or statistical analysis for trials they might design themselves. Training and technical assistance in this area could be potentially supported.

Potential projects

- Phase 1, 2, 3, and 4 studies of contraceptives
- Phase 1, 2, 3, and 4 studies for STI indications of microbicides (effectiveness trials of HIV prevention are not feasible due to the lack of appropriate study population in Moscow at this time).

RESEARCH CENTER OF MOLECULAR DIAGONOSTICS AND THERAPY

Staff persons interviewed:

Alexei Federov

Evgenii S. Severin, General Director; Head, Department of Biochemistry. E-mail: e.severin@mtu-net.ru

Peter G. Sveshnikov, Deputy Director. E-mail: svesh@aha.ru

This research center had 600 people on staff in the past but is now down to 150 people (including about 95 at the PhD level). They have animal facilities, a 40–bed clinic, and an IRB, but are not licensed to do clinical drug trials. They have eight divisions,

including biochemistry and toxicology, and they are working on a variety of diagnostic technologies, including test kits based on monoclonal antibodies, polymerase chain reaction (PCR), and biosensors. They are also interested in targeted delivery systems for oncology, immunotherapy, and tuberculosis treatment. They have developed vaccine candidates for tuberculosis, HPV subtypes 16 and 18, and hepatitis C virus. They plan a solid dose formulation for the HPV vaccine that could be used for vaginal delivery. Their strength seems to be targeting drug and vaccine delivery to tissues where they can be most effective. Dr. Sveshnikov described a partnership with GD Searle to build a $24 million factory to make Searle products, but Pfizer now owns the program and the future is uncertain. USAID may have had a role in establishing this partnership. They have also partnered with PATH on a proposal to the Gates Foundation, which may be pending. They have many product leads that they hope to move into clinical trials, and will follow FDA guidelines preclinically and clinically. ISTC funded the building of a small manufacturing center intended to produce clinical product supplies. The center does not currently work on contraceptive research and development, but Dr. Severin expressed confidence that they could develop a program if there were funds for it. They are also interested in probiotic products to maintain normal flora and thereby enhance vaginal health and disease resistance. They are looking for private sector partners, but were wary of working with Russian industry because they "take patents and leave." They also had little hope that the Russian regulatory environment would improve soon. They support their own research in part with proceeds from selling specialized monoclonal antibodies to pharmaceutical companies and they have a test strip (possibly for streptococcus) in partnership with a Finnish firm.

Potential product candidates

- Novel drug delivery systems
- Gene therapy
- Novel approaches to immunology/oncology: DNA vaccines, gene therapy, dendritic cells, xeno-transplants
- Antisense oligonucleotides
- Immuno-filtration and enzyme diagnostic kits
- Life extension products
- Anti–HPV vaccine (fused recombinant protein)
- Ovarian and prostate cancer
- Epidermal Growth Factor with Taxol to treat breast cancer
- Recombinant hepatitis C and tuberculosis vaccines
- Improved HPV diagnostics
- Anti-epithelial carcinoma preparations

INSTITUTE OF PHYSICAL–CHEMICAL MEDICINE

Staff persons interviewed:

Vadim M. Govorun, Deputy Director. E-mail: govorun@hotmail.ru
Vassily N. Lazarev, Head of Laboratory

Recombinant vectors have been obtained, which express the gene for the antimicrobial peptide Melettin, and the plasmids were administered using cationic liposomes. The effect observed was inhibition of infections caused by mycoplasma hominis, chlamydia

trachomatis (in cell culture and in mice), as well as by mycoplasma gallisepticum (in broiler chickens). The institute reports to the Russian Ministry of Health, and has been established to provide a range of physical, chemical, and molecular biology methods to assist health care services. The institute is engaged in studying drug efficacy.

The institute has operated a spin-off company, called Lytech, since 1992 and has an extensive product catalog (which the team received) of laboratory reagents that they have developed, plus some laboratory equipment from international manufacturers as well. They market in Russia and other CIS countries. Lytech also operates a clinical testing laboratory where they conduct about 50,000 tests per month. Five percent of the profits goes the institute, but the company also supports product research and development for some selected leads as well. They feel their products are gold-standard quality and comparable to any available worldwide, but their marketing efforts are limited by their staff and time. One of their PCR test kits was evaluated in Sweden and had good correlations with other products available. They also provide diagnostic testing and pathogen genotyping for hospital clients and would like to expand a gonorrhea surveillance program to all of Russia. The MOH provides some financial support for this.

Potential product candidates

- PCR technology test kits for STIs
- Melettin as an antimicrobial peptide; agricultural applications
- Anti-chlamydia drugs
- Inhibition of sexually transmitted infections with peptide microbicides

G. GAUZE STATE INSTITUTE FOR NEW ANTIBIOTICS, RUSSIAN ACADEMY OF MEDICAL SCIENCE

Staff persons interviewed:

Alexander A. Firsov, Head, Department of Pharmacokinetics and Pharmacodynamics.
E-mail: firsov@dol.ru
Maria N. Preobrazhenskaya, Deputy Director. E-mail: mnp@space.ru

The Gauze Institute is over 50 years old and currently employs about 170 people. The institute is almost entirely supported on a grant basis, including grants and collaborations with ISTC on new antibiotics for dangerous diseases and immunomodulators. This is the only institution in Russia that performs a wide search for new antibiotics. The institute possesses a large collection of microorganisms, predominantly actinomycetes. The institute's founder, Professor Gauze, discovered gramicidin C in 1942. Since then, about 15 novel antibiotics of all classes, including anti-tumor drugs, have been discovered at the institute. Main research areas include the biology and genetics of drug producers, pharmacodynamics of drugs, chemical transformation of known antibiotics, and search for new producer strains. The institute also performs preclinical testing of efficacy of various drugs, although they are not doing GLP–compliant studies. They conduct many PK studies for generic drugs—which they said were about 90 percent of the products currently brought to market.

The institute carries out work on development of ingenious preparations of a novel type that prevent the entry of HIV–1 and HIV–2 viruses into the cell. An international patent on preparations of this kind was issued to the institute in 2004. Chemical transformation of a novel antibiotic discovered at the institute results in the formation of an active anti–AIDS substance.

A new preparation named Ascorbinogen has been developed and studied at the institute. This preparation is a powerful and unspecific immunomodulator, capable of preventing death of laboratory animals from bacterial and viral infection following oral administration. Its mechanism of action is associated with stimulation of Paneth's cells in the intestine and activation of production of endoantibiotics by them, as well as with stimulation of neutrophils. The product is a natural product released from cabbage, cauliflower, broccoli, and kohlrabi. It is available in health food stores in the United States and is not patentable, so they are working on derivatives, which would maintain antiviral and antialopecia properties. They have a Russian but not United States patent on a new derivative. It appears to have interesting antiviral activity and potential microbicide applications because it stimulates endogenous protegrin release.

This institute has a long history of developing antibiotics, some of which are still in production and used therapeutically. The new Aramomycin product they have developed is similar to Vancomycin and is being reviewed by the State Pharmaceutical Board for clinical testing. They expect it to be tested and registered as a product in Russia in about a year. They are looking at derivatives that would be effective against Vancomycin-resistant bacteria. They have had a collaborative relationship with Eric DeClerque in Belgium for many years, have occasionally exchanged visits, and have some interesting leads on anti–HIV agents. Some of the leads have international patents and they are looking for product development partners. ISTC funds have allowed them to collaborate with organic chemists (it is not clear who received the funds) and to purchase an HPLC system. They can do a variety of testing in small animals, including toxicology and pharmacokinetics, but it is not GLP. Other collaborations have included Brown and Harvard universities, the University of California, Berkeley, NIH, and a private company in New Jersey. They have scientific agreements with a number of organizations in Belgium, Sweden, France, Hungary and others; the grants being registered through their Department of Foreign Affairs. Although this institute has had difficulties in recent years like others, these investigators seemed to be quite productive on the basis of the international collaborations they have developed and the strength of the resulting research. They identified new equipment and new students as things they needed most.

Potential product candidates and collaborations

- Aramomycin: Glyco-peptide antibiotics with GP120 receptor inhibition, produced by a company in Moscow who organized the clinical trials.
- Ascorbigen: anti–STI, anti-hair loss following cancer therapy.
- The Gauze Institute is interested in collaborative research in the following areas:
  - the institute has a potential to set up synthesis of novel substances and for chemical transformation of natural antibiotics, as well as for their biological (antimicrobial or anti-tumor) testing; and

- microbicides preventing the transmission of AIDS and other sexually transmitted diseases.

MOSCOW REGIONAL INSTITUTE OF OBSTETRICS AND GYNECOLOGY

Staff persons interviewed:

Elena Bulycheva, Head of Family Planning Center. Cell phone: 89169240630
Lela R. Kavtaladze, Head of International Liaison Department. Cell phone: 7-095-136-8793, E-mail: kavteladze@mail.ru

The Moscow Regional Institute of Obstetrics and Gynecology is the Ministry of Health institute providing reproductive health services to women in the Moscow region. Like the Research Center of Obstetrics, Gynecology and Perinatology, it is a leading clinical, research, and training organization in reproductive health in Russia. The Moscow Regional Institute is comprised of five departments: Obstetrics, Gynecology, Gynecological Endocrinology, Endoscopical Surgery, and Urogynecology. The Family Planning Center was organized in the institute in mid–1990s; at least 2,000 women receive family planning services a year. Their services are free of charge for women from the Moscow region, and on a fee-for-service basis for those from outside the Moscow region.

International collaborations include the Soros Foundation, CRDF (funded project "Congenital malformations and alcoholism"), and the Italian and Canadian embassies.

Due to the existing relations between the health authorities of the Moscow region and the institute, the institute can implement educational or interventional projects in the entire region and monitor and evaluate effects on public health. For example, one of the projects sponsored by Gedeon Richter (the Hungarian pharmaceutical company) led to the reduction of abortion rates among adolescents from 2 percent to 1.6 percent in two years. The project included different educational, counseling and clinical interventions aimed at preventing abortion and the higher utilization of modern methods of contraception among Moscow region adolescents.

The institute is licensed to conduct clinical trials, and has been involved in conducting GCP trials for pharmaceutical companies for 10 years. The products under evaluation included contraceptives, antibiotics, hormone replacement therapies and products for osteoporosis/osteopoenia. All research staff involved in clinical trials have been trained in GCP. Their trials with the pharmaceutical companies are monitored by international clinical research organizations, so the institute staff is familiar with the international standards and processes.

The main research interests expressed by Dr. Lela R. Kavtaladze, Head of International Research Services, with whom we met are: behavioral aspects of contraceptive use; clinical testing of contraceptives in accordance with GCP regulations; hormone replacement therapy; osteoporosis; and, testing of products for STI prevention.

Potential projects:

- Phase 1, 2, 3, and 4 studies of contraceptives
- Phase 1, 2, 3 and 4 studies or STI indications of microbicides
- Effectiveness trials of microbicides using HIV transmissions as an endpoint are not feasible due to the lack of appropriate study population, a topic addressed further in the full report
- Use of key staff, such as Dr. Kavtaladze, for expanding training to other regions of Russia, and possibly developing country programs

CENTER OF MODERN MEDICAL TECHNOLOGY (TEMPO)

Staff persons interviewed:

Natalia Popova, TEMPO Associate
Yuri V. Remnev, Deputy Director. E-mail: remnevYV@yandex.ru; remnev@nptemp.ru

TEMPO is a recently established consortium of research institutes intended to provide one-stop shopping for funders initiating biotechnology projects in Russia. TEMPO represents eleven major research institutes.

Potential product candidates

- Holding a "Business Plan Competition" for investor presentations

InfaMed (and Prevention, an affiliated NGO)

Staff persons interviewed:

Yuri S. Krivoshein, President
Igor V. Smirnov, Head of Medical Department. Phone: 7-095-324-8209,
E-mail: i_sm@mail.ru

It was explained that in the 1970s the Soviet space program supported a lab in Ukraine with 50 researchers to develop a product for cosmonaut hygiene. The lab synthesized and evaluated hundreds of leads. After the space research declined, they developed Myramistin as a protective and curative product with activity against various pathogens, including STIs. It was distributed during the 1980 Olympics in Moscow to prevent sexually transmitted infections from abroad, reportedly with good effect. It was then provided to 300 taxi drivers for their personal protection and another 300 taxi drivers who did not use it were used as a comparison group. The users had two cases of STDs in the following year and the non-users had 20. Some other studies were done and it was patented for STI protection and approved for marketing in 1991. Activity was cited against gram positive and negative bacteria, HSV, HIV, candida and other fungi, and trichomoniasis and other protozoa. Although it is said to work like other surfactants, it was also said to have minimal toxicity at low concentrations. Reportedly, 7–8 percent of men have pain with application that lasts 15–30 seconds. It is recommended that men use the entire package, which costs about $2, but men typically use one package for three or four applications. Women have no pain or other symptoms. Myramistin is also patented as a contraceptive in gel and suppository formulations. The suppository is not available yet, but the gel is now being tested for contraceptive effect in 20 couples, 15 of whom

have completed, with no pregnancies in 20 months. There were no changes in microflora or pH and no side effects. They are planning a larger test with 100 couples that would be coordinated by the State Pharmaceutical Committee and funded by InfaMed. The trial will start in 2006 and be finished one year later. It should be noted that these trials are not large enough to be considered pivotal in determining contraceptive effectiveness. In 2002–03, they had a private donor to support a trial for HIV prevention that would have been done in high-risk groups in Moscow following a WHO model protocol. In 2003, however, the Russian legislature removed the tax break the donor would have received and the deal could not be completed.

A paper on Myramistin was presented at the International AIDS Conference in 1998 in Geneva. Myramistin is also described as having immuno-modulatory effects and to promote wound healing. It has been tested extensively for bed sore therapy with good results. The assessment team received samples of the liquid wash formulation in the packages for men and women as well as the ophthalmic ointment. It is also available as a sexual lubricant. Women use the wash more often than the lubricant. A new GMP factory will be completed in 18 months in Moscow to increase production. The products will be registered in China by September 2005 and marketed by a private company there. (It was indicated that Russian law will require all pharmaceutical manufacturing in Russia to meet GMP standards in 2006.)

Product

- Myramistin: a surfactant with purported anti–STI, anti–HIV/AIDS, contraceptive, microbicide, burn therapy, bed sore, and eye ointment indications when applied as a spray, gel, aerosol or solution.

OTT INSTITUTE OF OBSTERICS AND GYNECOLOGY, RUSSIAN ACADEMY OF MEDICAL SCIENCES

Staff persons interviewed:

Igor Kogan, Scientific Secretary. E-mail: ikogan@mail.ru
Alevtina M. Savicheva, Head, Microbiology Laboratory. E-mail: savicheva@mail.ru
Sergey Selkov, Head, Laboratory of Immunology. E-mail: selkovsa@mail.ru
Marina Tarasova, Deputy Director. E-mail: tarasova@ott.ru

The Ott Institute is a leading Russian research organization in the field of obstetrics and gynecology. The major research areas at the institute are ecology and reproductive health, perinatology, pre- and postnatal care, high-risk pregnancies in women with extragenital pathology (diabetes, hypertension, etc.), and fertility control. The institute performs a wide range of diagnostic and treatment procedures on a commercial and free-of-charge basis. The institute is a leading teaching facility conducting various training programs for medical and graduate students and physicians of St. Petersburg, the St. Petersburg region and the northwest region of Russia.

The Ott Institute has been working extensively with international organizations in the field of reproductive health, contraception, and sexually transmitted diseases. It has a decade-long history of collaboration with USAID. A family planning center was created at the institute in 1996 with financial support from USAID and technical assistance from

JHPIEGO and AVSC International (now EngenderHealth). On the basis of this center, a number of projects on reproductive health have been carried out with such United States organizations as Futures Group, EngenderHealth, Open Society Institute, JSI, Inc., and others.

Clinical testing of efficacy and safety of various drug products in accordance with internationally accepted protocols is currently under way at the institute. The projects are funded by various (mostly European) pharmaceutical companies and are monitored by large clinical research organizations (e.g., PSI, Quintiles). They have a local IRB that meets every two months, and more often if needed.

They currently have seven trials ongoing, with five additional studies under consideration:

- hormone replacement therapies,
- treatments for osteoporosis,
- insulin therapies during pregnancy,
- treatment for post-partum anemia, and
- inteferons for treating hepatitis C.

The institute's priority is to provide medical care to pregnant women and women with a wide range of genital disorders. Thus the main purpose of other research units and labs in the institute is to support this clinical work. However, most of the labs have developed their own, sometimes rather sophisticated, research agendas.

The microbiology laboratory meets the highest world standards for equipment and processes used in STD diagnostics. The laboratory has been engaged since 1998 in an international project aimed at improving the diagnostics and therapy of sexually transmitted diseases throughout the St. Petersburg region (or Leningradskaya Oblast). The project has been conducted in accordance with WHO recommendations and standards. Coordinators of the project are, from the Swedish side, Dr. M. Domeika, and from the Russian side, Professor A.M. Savicheva, Head of the Laboratory. This project is one that should be explored further in the context of our assessment to determine how this work could coordinate with activities of the U.S. CDC in Moscow and then how the training approach might be applied to technical assistance in developing countries.

Research areas of interest to staff at the Ott Institute include:

- clinical testing of contraceptives and microbicides
- STIs: methods of diagnosis and treatment, and resistance to antibiotics
- research in the areas of hormone replacement therapy and osteoporosis
- benign breast disorders of reproductive age

Potential projects:

- Phase 1, 2, 3, and 4 studies of contraceptives
- Phase 1, 2, 3, and 4 studies of microbicides using STIs as endpoints (effectiveness trials of microbicides using HIV transmissions as an endpoint are not feasible due to the lack of appropriate study population, a topic addressed further in the full report).

- The excellent facilities and research potential of the microbiology lab can be used for both lab support for clinical trials and for independent research in the area of STI diagnosis and treatment (e.g., HPV–related research).

PAVLOV STATE MEDICAL UNIVERSITY

Staff persons interviewed:

Dmitry Lioznov, Director, Center for Preventive Medicine. E-mail: lioznov@spmu.rssi.ru
Malikov, Director, Clinical Trials Unit
Tatyana Medvedeva, Member, Ethical Committee
Edwin Zvartau, Vice-Rector for Research. E-mail: zvartau@spmu.rssi.ru

Pavlov State Medical University is mainly an educational organization (about 40,000 doctors graduated in the course of last 20 years), but it also has significant research and treatment facilities. Major research departments included cardiovascular, pharmacology, nephrology, hematology, immunology, and laser medicine. Subjects include reproductive health, behavioral aspects, clinical testing of contraceptives and microbicides, training courses for STD prevention, epidemiology of STD, and monitoring of contraceptives in use. The university is actively engaged in research, training and clinical programs devoted to reproductive health and behavior, and in prevention of STIs, including AIDS and viral hepatitises. The university staff carries out epidemiological studies aimed at assessing the incidence of various diseases, including STIs. A part of these studies is concerned with behavioral features and social characteristics of target groups.

The university develops and conducts training programs for students and postgraduate students, for workers of medical clinics and for nongovernmental employees. Among programs related to STIs and reproductive health, one should mention *A Training Program to Facilitate the Integration of HIV Prevention into Primary Care in St. Petersburg, Russia*, carried out in Russia in 2003 under sponsorship of the World AIDS Foundation for the North-West region of Russia, as well as the new *Seminars on STIs and HIV/AIDS Prevention* for college students on prevention of STIs, developed with support from the Ford Foundation.

The university possesses extensive expertise in preclinical testing in the fields of pharmacology and toxicology of medicines, and is an expert center of the Russian Federation Ministry of Health, as well as a developer of federal standards documentation on protocols for preclinical testing (experimental studies) of a number of groups of pharmaceuticals. In the last 15 years the university, together with Valdman Institute of Pharmacology, is engaged in collaborative scientific and contract research with a number of large pharmaceutical companies (Novartis, Pierre Fabre, Bayer, Merck, Abbott, and some others). The Laboratory of Behavioral Pharmacology has been certified according to the preclinical studies standards of the European Community.

The university is now being considered as a partner of the UNICEF project "Invitation to the Future" to be launched in the spring of 2005 and aimed at improving the reproductive health of the younger generation.

Among the areas of study mentioned by the assessment team, the most interesting for the university are clinical testing of novel contraceptives and microbicides, surveillance and epidemiological studies of currently used contraceptives, behavioral and social aspects of contraceptive and microbicide use, as well as provision of training and infrastructure. Studies along these lines may be done as a continuation of the current programs run at the university, or serve as foundations for new avenues of activity.

Study projects

- Mechanism of drug-conditional behavior changes
- Naltrexone effects
- Neurocognitive function in drug addicts
- Effect of HIV prevention in developing countries
- HIV and alcohol use interactions
- HIV/hepatitis and tuberculosis interactions, especially in adolescent populations
- Prevalence of HIV and sexually transmitted infections in adolescents

STATE RESEARCH INSTITUTE OF HIGHLY PURE BIOPREPARATIONS

Staff persons interviewed:

Sergey A. Ketlinsky, Deputy Director in Science. E-mail: ketlinsky@inshpb.spb.ru
Kolobov, Head, Lab of Synthetic Peptides
Andrey S. Simbirtsev, Head, Laboratory of Immunopharmacology. E-mail: simbirtsev@hpb.spb.ru, sim@inshpb.spb.ru

Originally, the institute was primarily involved in aerosol research, but has shown initiative and skill in expanding its capabilities. It has experience in the full product development cycle, from research to production.

This institute markets a variety of gene-engineered products; some are for clinical use, including resins to remove cytokines from blood outside the body, analytical resins, and therapies for the upper respiratory tract. They produce the products in their own laboratories. They have six or seven grants for international collaborations, e.g., with Massachusetts General Hospital and other United States partners, some of which are funded by CRDF and have good support for travel and for sponsoring major international meetings in Russia. A Bio-Industry Initiative grant is ending. They are working on monoclonal and polyclonal antibodies to use for passive immunization against tuberculosis. They indicated that many good ideas cannot be pursued because they do not have sufficient funds.

They have a staff of 260 with about 100 scientists. As elsewhere, the state covers modest salaries, and the sale of products supports the research. They market some items abroad in India, China, and Italy, but they do not have the required clinical trials to register many of their products abroad and do not plan to pursue this. They consider themselves to be a research institute and not a pharmaceutical company. They collaborate with a toxicology facility in St. Petersburg that is being upgraded to international standards with ISTC funds and rely on the State Pharmaceutical Committee when clinical testing is needed.

Their potential interest in microbicides is based on new antimicrobial peptides they are developing with CRDF support, some of which are as small as 12 amino acids and have broad spectrum activity. These are considered to be of scientific interest and are not part of a product development plan at this time. They have a theoretical interest in immuno-contraception as well. They cited plans by the Russian government to reduce the number of research institutes nationwide to 300, from about 3,000 in 1990. They expect the political, professional, and personal consequences to continue to be very difficult, but hope that their institute will survive.

Potential product candidates

- Recombinant receptor antagonists
- Fermentation production for gene expression
- Resins for cholesterol elimination
- Interferon applications in the respiratory tract
- Passives immunization, as for treatment of pseudomonas
- Selling: cytokines, erythropoietin, beta interferon, interleukin
- Oral anti-tuberculosis preparation; ready for clinical testing in 2006
- Peptide-based anti–HIV/AIDS vaccine
- Peptide antimicrobials
- Diagnostic kits of hepatitis C, HIV/AIDS, herpes virus, syphilis, and cytomegalovirus
- Early interest in immuno-contraceptive

INSTITUTE OF CYTOLOGY, RUSSIAN ACADEMY OF SCIENCES

Staff persons interviewed:

Tamara V. Beyer, Head of Research Group
Sergei N. Borchsenius, Head of Genome Structural Organization
Valeri A. Pospolov, Head of Laboratory of Molecular Mechanisms of Cell Differentiation
Sergei O. Skarlato, Deputy Director for Science and Head of Laboratory of Unicellular Organisms

The institute addresses HIV/AIDS and associated infections, as well as monitoring and preventive measures. For a number of years a scientific group (headed by Professor Tamara Beyer) in the laboratory of unicellular organisms has been engaged in studies of the cellular and molecular biology of cryptosporidia and microsporidia, protozoan agents of AIDS–associated infections. Unfortunately, the incidence of these diseases has not received sufficient attention, in contrast with the situation in many other counties of the world. Thus, in the United States, cryptosporidiosis is recorded in 10 percent of AIDS patients, and in the developing world, in 30 percent of the cases. To improve the situation, the institute, together with the State Institute of Highly Pure Biopreparations (in St. Petersburg), has applied for a CRDF grant for a project entitled "Establishing the incidence of opportunistic pathogens, microsporidia and cryptosporidia, among HIV/AIDS–infected patients in Russia." If the study identifies a significant incidence of these infections in St. Petersburg, prevention and treatment of the patients will become an urgent issue. It should be noted that there are no effective microbicides against protozoan infections. For instance, nitazoxanide, which is effective against HIV in-vitro, is only

used to treat cryptosporidiosis in children, whereas fumagin is effective against one out of four microsporoidosis species found in man. Thus, the issue of treating cryptosporidiosis and microsporoidosis in AIDS patients and in people with normal immune systems is still unresolved, and requires a joint effort of different specialists. Experience of the institute suggests that the development of drugs active against cryptosporidiosis and microsporoidosis should be based on the specific features of their intracellular growth and their exceptional ability to suppress the protective mechanisms (e.g., the lysosomal digestion) of the host cell.

The institute also performs DNA diagnostics and endocrine analyses on a contract basis for local clinical facilities and government agencies. They have submitted a CRDF proposal to continue this work on subclinical infections with cryptosporidium. This institute had observed such opportunistic infections in the late 1980s but was not allowed to mention HIV or AIDS in publications at that time. They cited support from the Soros Foundation and from INTAS in the 1990s as crucial to retain key scientists in their group who otherwise would have emigrated. They continue to work with many colleagues outside of Russia. They also have several small grants of less than $10,000 from the Russian Foundation for Basic Research (a foundation the assessment team did not hear about elsewhere) and some funds from the Ministry of (Education and) Science. They also said that the Presidium of the National Academy of Sciences awards sizable grants (maybe $100,000) for research, but only about 10 awards per year nationwide. Their staff has been greatly reduced in the last 10 years, but they expected to survive. They thought that other institutes, in rented space or with valuable central city property, were more likely to be closed.

THE BIOMEDICAL CENTER, St. Petersburg State University

Staff person interviewed:

Andrei P. Kozlov, Director. E-mail: biomed@mailbox.alkor.ru,
contact@biomed.spb.ru.

In February 2005, the Yale School of Public Health's Epidemiology of Microbial Diseases Division, and The Biomedical Center in St. Petersburg, Russia, announced a partnership to develop the Tuberculosis–AIDS Clinical Training and Research Unit (the Tuberculosis–AIDS Unit) in St. Petersburg, Russia. This partnership is funded by a five year, $3 million International Clinical, Operational, and Health Services Research Training Award for AIDS and Tuberculosis (ICOHRTA–AIDS/TB) from the Fogarty International Center.

Professor Andrei Kozlov, Director of the Biomedical Center, has previously been an investigator in the HIV Prevention Trials Network. He and collaborators from Yale, Johns Hopkins, and UNC are competing for one of the site grants in the reorganized microbicides and HIV prevention networks.

STELLIT

Staff persons interviewed:

Larisa Gareeva, Project Manager. E-mail: lagar@bk.ru.
Maia Rusakova, Director. E-mail: maia_socio@hotmail.com, maia@spbstellit.ru

Stellit is an NGO that conducts behavioral research related to the HIV/AIDS epidemic. Due to a conflict of schedules we did not meet with Maia Rusakova, director of Stellit.

YUVENTA

Staff person interviewed:

Pavel N. Krotin, Director

Yuventa is an NGO targeting reproductive health of adolescents in St. Petersburg. The clinic was founded in 1992 and it is providing a wide range of free-of-charge reproductive health services to adolescents of St. Petersburg.

Yuventa has extensive prior and ongoing collaboration with international donors (e.g., UNICEF, WHO, USAID, and IPPF) and agencies working in the area of reproductive health of youth and adolescents.

The clinic is licensed to conduct Phase 3 and 4 clinical trials. It has been involved in a number of GCP–regulated trials conducted by big pharma through international clinical research organizations. Products under investigation: Depo-Provera for self-injection, Interferon for hepatitis C.

Areas of interest include projects aimed at reproductive health education among adolescents; they are looking for additional funding to continue successful projects. J&J used to sponsor a program where volunteers trained at Yuventa, would go to summer camps and provide education in self-hygiene, reproductive anatomy and physiology, etc. The project was terminated due to lack of funding.

APPENDIX D

ORGANIZATION CAPABILITIES

ORGANIZATION CAPABILITIES

Organization	Fundamental Research	Vaccine/Biological Syn.	Nonclinical	Phase 1 Clinical	Phase 2–3 Clinical	Phase 4 Clinical	Clinical Treatment or Screening Program	Outreach	Training	Product Candidate Development	Pilot Plant Synthesis	Production Facility	Marketing
Moscow Medical Academy (through affiliates)	X		X	X	X	X	X		X				
SANAM					X[1]	X	X	X	X				
Ivanovsky Institute of Virology	X	X	X								X		X
Institute of Protein Research	X	X											
Biological Testing Laboratory			X										
Institute of Physiology and Biochemistry of Microorganisms	X	X	X		X					X	X		
Center for Maternal and Child Health				X	X	X	X		X				
Research Center of Molecular Diagnostics	X		X							X	X	X?	
Institute of Physical-Chemical Medicine	X	X	X										X[2]
G. Gauze State Institute	X	X	X								X[3]		
Moscow Regional Institute of Obstetrics and Gynecology				X	X	X	X		X				
TEMPO										X			
InfaMed			X		X	X				X			
Ott Institute of Ob/Gyn				X	X	X	X		X				
Pavlov State Medical University	X	X	X	X	X	X	X		X				
Institute of Highly Pure Biopreparations	X	X	X							X	X	X[4]	X
Institute of Cytology	X		X										
Biomedical Center					X		X		X				
Stellit								X					
Yuventa					X	X	X	X	X				

[1] SANAM is not completely ready to participate in Phase 2–4 trials. It needs to obtain a license and the staff needs to be introduced and trained in GCP, research ethics, etc.
[2] via Lytech
[3] Inactive
[4] Non–GMP

APPENDIX E

ORGANIZATION SOURCES OF FUNDS

ORGANIZATION SOURCES OF FUNDS

Organization	Federal	USAID	CDRF	ISTC/BII/BTAP	Other Grants	Contract Research	Donations	Collaborations with International Institutions	Fee for Service	Product Sales	Angel/Venture Capital
Moscow Medical Academy (through affiliates)	X				X	X		X			
SANAM		X	X		X	X	X	X	X	X	
Ivanovsky Institute of Virology	X		X	X	X	X		X			
Institute of Protein Research	X		X		X	X		X			
Biological Testing Laboratory	X	X	X			X					
Institute of Physiology and Biochemistry of Microorganisms	X	X	X					X			
Center for Maternal and Child Health	X					X		X	X		
Research Center of Molecular Diagnostics	X	X	X	X		X		X		X	
Institute of Physical-Chemical Medicine					X						
G. Gauze Institute	X			X	X	X		X			
Moscow Regional Institute of Obstetrics and Gynecology	X[1]		X			X		X	X		
TEMPO			X	X	X						
InfaMed	X									X	X
Ott Institute of Ob/Gyn	X				X	X		X	X		
Pavlov State Medical University	X		X		X	X	X	X	X		
Institute of Highly Pure Biopreparations	X		X	X	X	X				X	
Institute of Cytology	X		X		X						
Biomedical Center					X		X	X			
Stellit							X	X			
Yuventa	X[2]	X			X	X		X	X		

Note: Funding sources indicated represent recent, current, or near-term expected sources of funds.
[1] From the Moscow Region
[2] From the city of St. Petersburg

APPENDIX F

PROCEDURES FOR DRUG REGISTRATION

PROCEDURES FOR DRUG REGISTRATION

(Summarized from the Russian Federation Law on Medical Products, 1998)

Regulatory Requirements

a) Preclinical studies

- Preclinical studies of drugs are carried out by developers of the drug according to laboratory practices approved by the federal authority for drug quality control;

- Preclinical studies are conducted according to an approved plan, with recording of the results in a protocol and issuing a report. The developer then issues a report on the possibility of conducting clinical trials in the future; and

- Preclinical studies using animals are conducted according to international regulations. The observance of regulations and ethical rules is monitored by the federal authority for drug quality control and regional authorities for drug quality control.

b) Clinical studies

- The decision to conduct clinical trials for a medical product is taken by the federal authority for drug quality control based on the following submitted documents:
  - a written request from the drug developer;
  - a positive decision of the ethics committee at the federal authority for drug quality control;
  - a report on the preclinical study of the medical product;
  - instructions for use of the medical product;
  - clinical trials of medical products are carried out at medical institutions that are licensed to do so. Note: The Russian Federation Law on Licensing of Certain Types of Activity, of August 2001, with amendments of 2002 and 2003, does not include the requirement to license medical institutions to conduct clinical trials. This appears contradictory to the 1998 Law on Medical Products and, depending on which law takes precedence, may allow any medical institution to conduct clinical trials, creating ambiguity about which several institutes have complained in follow-up interviews;
  - the licenses to conduct clinical trials are issued by the Federal Ministry of Health to ensure compliance with the approved clinical practices; and
  - the list of licensed medical institutions is published.

- The legislative basis for clinical trials of a medical product consists of
  - A decision of the federal authority for drug quality control to conduct clinical trials and
  - A contract to conduct clinical trials between the drug developer and the medical institution.
  - The contract on conducting clinical trails should contain
    - information on terms and volume of clinical trials of the medical product,

- total cost of the clinical trails program,
- the form in which the results should be submitted to the federal authority for drug quality control, and
- health insurance conditions for patients involved in clinical trials.

- Funding of clinical trials by the drug developer is done by paying the invoice issued by the medical institution, according to the contract on conducting the clinical trials;
- direct payments by the drug developer or any other legal or physical persons to the staff of the medical institution which conducts the clinical trials is forbidden.

- The clinical trials program is subject to approval by the head of the medical institution.

- The program must be developed with the participation of the institution's ethical committee.

- The head of the trials program must be fully informed on the results of the preclinical studies of the medical product.

- The head of the program is responsible for the choice of human subjects to be involved in the trials.

- The report on the trials is compiled by the head of the trials program.

- Clinical trials may be discontinued if a threat to the health of human subjects is discovered in the course of the trials. This decision is to be made by the head of the trials program.

APPENDIX G

REFERENCES

REFERENCE MATERIALS

Note: All reference materials noted are on file at USAID/Washington.

Biological Testing Laboratory, Branch of Shemyakin & Ovchinnikov Institute, Russian Academy of Science. (Undated brochure)

Center for Ecological Research and BioResources Development, Pushchino, Russia. (Undated brochure)

Civilian Research and Development Foundation. "Development of Joint U.S.–Eurasian Research Agendas in HIV/AIDS and Related Infections." Workshop, Moscow, Russia, November 15–17, 2004.

Consolidated Site Visit Report: Moscow/St. Petersburg, Russia, November 13–21, 2004.

"Control and Prevention of Sexually Transmitted Infections." Conference, April 22–23, 2004, St. Petersburg, Russia, Volume LIII, Supplement April 2004.

Development of Joint U.S.–Eurasian Research Agendas in HIV/AIDS and Related Infections. Moscow, Russia, November 15–17, 2004.

Development of Joint U.S.–Eurasian Research Agendas in HIV/AIDS and Related Infections. Workshop final report. (No date)

Historical Overview-Biological Weapons Development in the Soviet Union and Russia. (No date)

G.K. Skyrabin Institute of Biochemistry and Physiology of Microorganisms, RAS. "LISOAMIDASE. Novel Antibacterial Enzyme Drug." Pushchino, Russia. (No date)

InfaMed. 2004–2005 Product Catalog. (Russian language document)

_____. Myramistin Product Brochure. (Russian language document, no date)

John Snow, Inc. "Russia Health Care Improvement, Maternal and Child Health Initiative (MCH)." Boston, Massachusetts, April and October, 2004.

_____. "Strengthening and Expanding Reproductive Health and Family Planning Services. Maternal and Child Health Initiative." Boston, Massachusetts, 2004.

Kaiser Network. "HIV Spreading Rapidly in Russia." March 16, 2005.

Krivoshein, Y.S., A. Rudjko, I. Smirnov, and V. Svistov. "Antiseptic Myramistin in the Treatment and Prevention of Sexual Transmitted Diseases" (CD). JSC, InfaMed, Moscow, Russia, March 18, 2005.

Lazarev, V.N., T. Parfenova, S. Gularyan, O. Misyurina, T. Akopian, and V. Govorun. "Induced Expression of Melittin, an Antimicrobial Peptide, Inhibits Infection by *Chlamydia Trachomatis* and *Mycoplasm Hommis* in a HeLa Cell Line." *International Journal of Antimicrobial Agents*, 19:133–137, 2002.

Lazarev, V.N., L. Stipkovis, J. Biro, D. Kiklodi, M. Shkarupeta, G. Titova, T. Akopian, and V. Govorun. "Induced Expression of the Antimicrobial Peptide Melittin Inhibits Experimental Infection by *Mycoplasma Gallisepticum* in Chickens." *Microbes and Infection*, 6:536–541, 2004.

Maksimova, L. "Practical Advice on Registering and Certifying Pharmaceuticals in Russia." United States Commercial Service, U.S. Embassy, Moscow, Russia, 2003.

Misyurina, O.Y., E. Chipitsyna, Y. Finashutina, V. Lazarev, T. Akopian, A. Savicheva, and V. Govorun. "Mutations I a 23S rRNA Gene of *Chlamydia Trachomatis* Associated with Resistance to Macrolides." *Antimicrobial Agents and Chemotherapy*, 48:1,347–49, 2004.

The Ott Institute 1797–1997. (Undated brochure)

Research Center for Toxicology and Hygenic Regulation of Biopreparations. "DNA Vaccines as a Biosecurity Tool." Compact disk, Serpukhov, Moscow Region, Russia, March 15, 2005.

_____. "Facilities for Pre-clinical Trials in Accordance with GLP Requirements." Compact disk, Serpukhov, Moscow Region, Russia, March 15, 2005.

_____. "Information on the Center." Compact disk, Serpukhov, Moscow Region, Russia. March 15, 2005.

_____. Institute Brochure. Serpukhov, Moscow Region, Russia.

Ryadnov, M.G., O. Degtyareva, I. Kashparov, and Y. Mitin. "A New, Synthetic All-D–Peptide with High Bacterial and Low Mammalian Cytotoxicity." *Peptides*, 23:1,869–71, 2002.

Stellit. Organization Brochure. St. Petersburg, Russia. (Undated)

Stone, Alan. "Microbicide Research in Russia." London, U.K., 2004.

P. Bergman, Swedish Institute of Public Health. "A Ukrainian Medicine Against HIV is Being Tested in Sweden." *Hiv-aktuellt*, 1995.

U.S. Department of Defense. "Defense Threat Reduction Agency-Cooperative Threat Reduction Program." Brief. (No date)

USAID/Russia. "2003–2008 HIV/AIDS Prevention Operation Plan: Moscow, Russia." Brief, 2003.

_____. "USAID/Russia's HIV/AIDS Portfolio." Brief, Moscow, Russia, 2004.

_____ "USAID in Russia." Brief, Moscow, Russia, 2005.

U.S. Department of Health and Human Services Office of Global Health Affairs. Brief. (No date)

U.S. Department of State. "Bureau of Nonproliferation." Brief. (No date)

_____. "NP–BioIndustry Initiative (BII)." Brief. (No date)